UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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PUBLIC HEALTH SERVICE

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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DIVISION OF CARDIOVASCULAR AND

RENAL DRUG PRODUCTS

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CARDIOVASCULAR AND RENAL DRUGS

ADVISORY COMMITTEE

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MEETING

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Wednesday, January 28, 1998

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The meeting took place in the Natcher Auditorium, 45 Center Drive, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland, at 9:00 a.m., Milton Packer, M.D., Chairperson, presiding.

PRESENT:

MILTON PACKER, M.D., Chairperson

JOAN C. STANDAERT, Executive Secretary

JOHN DiMARCO, M.D., Member

MARVIN KONSTAM, M.D., Member

JoANN LINDENFELD, M.D., Member

LEMUEL MOYÉ, M.D., Member

ILEANA PIÑA, M.D., Member

DAN RODEN, M.D.C.M., Member

RAYMOND LIPICKY, M.D., FDA

WALID NURI, Ph.D., FDA Reviewer

DANIEL GRETLER, M.D., Sponsor Representative

ROBERT HARRINGTON, M.D., Sponsor Representative

MICHAEL M. KITT, M.D., Sponsor Representative

MICHAEL LINCOFF, M.D., Sponsor Representative

ALSO PRESENT:

ROBERT R. FENICHEL, M.D.

LLOYD FISCHER, Ph.D.

TOM FLEMING, Ph.D.

CHARLES GANLEY, M.D.

MARY ANN GORDON, M.D.

CHARLES HOMCY, M.D.

A.J. SANKOH, Ph.D.

ERIC TOPOL, M.D.

JANET WITHES

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

9:00 a.m.

CHAIRPERSON PARKER: If I could have everyone take their seats, please. We will be beginning this morning's presentation on NDA 20-718, the application is on Integrilin (eptifibatide). I must say that I have personal difficulties pronouncing the generic name of this drug, and I guess the committee, we have already discussed this, if the committee wants to refer to this product as Integrilin that's okay. We generally don't do that, but we generally don't like to mispronounce the names of drugs either. The sponsor is COR Therapeutics, and Joan will read the conflict of interest statement.

EXECUTIVE SECRETARY STANDAERT: The following announcement address the issue of Conflict of Interest with regard to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests and firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this

meeting with the following exceptions: Doctors Robert Califf, Cindy Grines and Udho Thadani are excused from participating in all matters concerning Integrilin.

In the event that the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they might wish to comment upon.

That concludes the Conflict of Interest statement for January 28, 1998.

CHAIRPERSON PARKER: We will now call for any public comments.

There being none, we'll ask the sponsor to proceed with their presentation on the evaluation of Integrilin for use in the setting of percutaneous transluminal angioplasty and acute coronary syndrome.

DOCTOR KITT: Good morning.

Members of the Advisory Committee, FDA officials, ladies and gentlemen, my name is Doctor Michael Kitt, and I am Vice President of Clinical

Research at COR Therapeutics.

It is my pleasure, on behalf of COR, to return to this committee to present the clinical study results of the evaluation of Integrilin, which has the generic name of eptifibatide, in the treatment of patients with unstable angina, non Q-wave myocardial infarction, and those patients undergoing coronary angioplasty.

Many of you on the committee recall that in February, 1997, we presented the results of the IMPACT II study, as the basis for approval for Integrilin for the prevention of acute ischemic complications in patients undergoing coronary angioplasty.

At that meeting, this committee voted that the IMPACT II study was a positive study, but that as a single study it was not sufficient for approval.

The FDA subsequently issued an action letter to COR indicating that a second study in a similar indication may add support to the findings of the IMPACT II study. We are, therefore, returning to present the data on this second study of Integrilin, the PURSUIT study.

This study, the largest study ever conducted in patients with unstable angina, non Q-wave myocardial infarction, demonstrated that Integrilin

was safe and effective in reducing the incidence of the irreversible endpoints, the composite of death and myocardial infarction.

We realize that we are presenting data from two studies in two different, but overlapping, clinical settings. As indicated in a passage from a recent draft guidance document from FDA, it is reasonable to consider these two conditions, these two studies as a similar pathophysiologic condition, that is, plaque rupture and thrombus formation, whether spontaneous, as in the acute coronary syndrome studied in PURSUIT, or induced as in the post-angioplasty studied in IMPACT II. Integrilin reduced the incidence of the severe irreversible and clinically-relevant outcomes, the composite of death in myocardial infarction in both of these studies.

In addition, there is considerable overlap in these two studies, as one quarter of the patients in the PURSUIT study underwent coronary angioplasty, and over one third of the patients in the IMPACT study presented with unstable angina.

It is also important to note that in both of these studies patient benefit was achieved with little safety risk, even though the studies were performed at different dosage levels.

We are, therefore, seeking approval for Integrilin for the prevention of death or myocardial infarction in patients with unstable angina or non Q-wave myocardial infarction and as an adjunct to coronary angioplasty for the prevention of acute ischemic complications related to abrupt closure of the treated coronary vessel.

There will be three presentations of data this morning. Doctor Daniel Gretler, Director of Clinical Research at COR Therapeutics, will briefly present the results of the IMPACT II study. He will then present data which provides the rationale for the dose selection in the PURSUIT study.

Doctor Robert Harrington, Assistant Professor of Medicine at Duke University, and one of the principal investigators of the PURSUIT study, will present the primary efficacy and safety results of the study.

Doctor Michael Lincoff, Assistant Professor of Medicine at the Cleveland Clinic Foundation, and a co-principal investigator of the PURSUIT study, will present data on patients who underwent percutaneous revascularization in the PURSUIT study, emphasizing the considerable overlap between PURSUIT and IMPACT II.

Finally, I will return to make some brief closing comments.

The following consultants are available to respond to questions from the committee: Doctor Eric Topol of the Cleveland Clinic Foundation, who was the PURSUIT study chairman; Doctor Judith Hochman of Columbia University, a PURSUIT Steering Committee member; and Doctor Kerry Lee from Duke University, who was the statistician for both the PURSUIT and the IMPACT II study; finally, Doctor James Tcheng of Duke University, a principal investigator of the IMPACT II study, is also available to respond to questions.

I'd like to invite Doctor Gretler to come up to present the results of the IMPACT II study.

DOCTOR GRETLER: Good morning.

Could I have the next set of slides, please? Thank you.

This presentation will contain three topics: first, a brief discussion of the pathophysiology of acute coronary syndromes, together with the pharmacology of GP IIB/IIIa inhibition and how the two relate to each other; second, the highlights of the IMPACT II study results; and, third, the rationale for the dose selection in the PURSUIT study.

My first topic deals with the common pathophysiology that exists for unstable angina, non Q-wave myocardial infarction on the one hand and the post-angioplasty state on the other. It also deals with the GP IIb/IIIa complex as a pharmacologic target, and lastly, with how the clinical pharmacology of eptifibatide fits in the therapy of acute coronary syndromes.

As you know, acute coronary syndromes are triggered by the rupture of an atherosclerotic plaque. This rupture can occur spontaneously, such as in unstable angina, but it can also occur after an intracoronary procedure such as PTCA. In either case, there is release of thrombogenic substances, platelet activation and platelet aggregation.

For this reason, or for these reasons, agents that inhibit platelet aggregation are being used in an attempt to prevent intracoronary thrombosis.

There are a number of agents that are in development or currently available that block one or more of the several stimuli and pathways that all lead to platelet aggregation, but there is one particularly attractive pharmacologic target, and that is the common -- the final common step of platelet

aggregation, the binding of fibrinogen to the GP IIb/IIIa complex.

GP IIb/IIIa inhibitors, including eptifibatide, inhibit the final obligatory step in the pathway of platelet aggregation. Eptifibatide is a small molecule that has a high affinity and high selectivity for the receptor. It has characteristics that are desirable for an acute care drug, namely, a very rapid onset of action and a short duration of action. This accounts for the rapid reversibility of its effects when it is discontinued, and also, we have been unable to detect antibody production against eptifibatide even after repeat administration to any given individual.

The IMPACT II study was the first major study we conducted with eptifibatide, it was reviewed one year ago by this committee and it is described in more detail in the briefing book. Briefly, IMPACT II demonstrated positive efficacy results and a good safety profile in patients undergoing PTCA.

IMPACT II was a large study conducted in the United States in patients who underwent elective or urgent PTCA. They all received standard therapy and they were randomized to one of three possible groups, placebo, or one of two similar eptifibatide

regiments, which both consisted of the same 135 micrograms per kilogram bolus and followed by either 0.5 or 0.75 micrograms per kilogram per minute infusion over 24 hours.

Overlap between this study and the PURSUIT study existed in the patient population, in the pathophysiology of the disease, and in the endpoint in that the components death and myocardial infarction were present in both studies as a primary endpoint.

This Kaplan Meier curve plots the occurrence of death, myocardial infarction or urgent interventions over 30 days following PTCA. In all our Kaplan Meier plots, the placebo group will be shown in the pale orange color here and the two eptifibatide groups in blue and green. The curves for the two eptifibatide groups look fairly similar until about five days after PTCA. After that, there is a small difference between the two groups. At 30 days, the primary endpoint, there was a 1.5 and 2.5 absolute percentage point reduction in the eptifibatide groups versus placebo. Thus, there was a reduction in the primary endpoint in both groups, one of which reached the protocol specified level of statistical significance, and this was obtained in the treated as randomized population.

This 48-hour Kaplan Meier plot examines the early time points. What can be seen on this figure is that most of the events occurred early after PTCA. In fact, 72 percent of all the events had occurred by the sixth hour after PTCA. What is also seen is, as expected, the full benefit of eptifibatide therapy occurred very early after the administration of the 135 microgram per kilogram bolus at the time of PTCA. And, I would also like to point out that the efficacy for the two eptifibatide regimens looked very similar throughout this observation period.

This is the Kaplan Meier plot for the irreversible endpoints, death and myocardial infarction, over six months. Six months was the long-term follow-up period that was specified in the protocol. This figure makes a number of points. The treatment benefit was maintained for at least six months. Also, the efficacy results for the two eptifibatide regimens are rather similar over the entire duration of the follow up. There is the same absolute 1.5 percentage point reduction at 48 hours, 30 days and six months. Of course, this is not unexpected given the similarity of the two eptifibatide regimens.

The safety profile of eptifibatide was very

good. The incidence of major bleeding, according to the TIMI criteria, was around 4.5 percent in all three groups. I should also point out here that the incidence of transfusions was very similar in all three groups.

I would now like to turn to the rationale for the dose selection that was used for IMPACT II and PURSUIT.

CHAIRPERSON PARKER: Can you pause for one moment and see if the committee has any comments on IMPACT II? John, any comments, John DiMarco, who is our primary reviewer.

DOCTOR DiMARCO: I had one question, in the protocol you had urgent interventions, which included stent placement, but I wasn't quite sure, you also allowed some elective stents during the protocol, even though they were discouraged. Who decided then whether the stent was elective, or urgent, or how they were placed?

DOCTOR GRETLER: With your permission, I would like to call Doctor James Tcheng, who was one of the principal investigators in the IMPACT II study, to answer any questions you might have on IMPACT II in particular.

DOCTOR TCHENG: Yes, I'm Doctor James

Tcheng from Duke University.

To answer your question, in the protocol, as part of the composite endpoint, urgent stent implantation for abrupt closure was considered an endpoint. However, elective stent implantation was not.

The adjudication of whether or not it was an urgent protocol-driven, protocol-endpoint event was determined by the Clinical Events Committee after review of the data that was provided to them post hoc, that is, the data was reviewed to determine whether or not it was considered to be elective or urgent because of abrupt closure.

DOCTOR DiMARCO: And, how many of each were there, do you remember? I think it's a small number.

DOCTOR TCHENG: It is a small number, I believe there was 32 or so were considered as endpoint events, with the majority, actually, 130 some odd stent implantations, considered to be as part of the process of care, if you will, that is, not an urgent endpoint type of an event. So, the majority of them were actually considered to be non-endpoint events.

DOCTOR DiMARCO: Okay.

And, considering that stent usage has increased over time, did you see a difference in stent

usage over the course of the protocol and, perhaps, could you project whether or not the same proportions of stents would be placed, or the same Integrilin and use would occur with current practice where stents are put in more widely?

DOCTOR TCHENG: That would be speculation. However, to set the time frame, the IMPACT II trial was conducted mostly in 1994, started in the late part of '93 and ended in the late part of '94, stents were just being approved in the summer of 1994, so it is true that as the protocol progressed, especially at the very end, we saw a few more stents placed.

The real answer to your question, I believe, is we really would have no way of knowing, with today's practice, because we do not have the clinical trials experience with Integrilin in the setting of coronary stent implantation, especially elective coronary stent implantation to address your question.

DOCTOR DiMARCO: Okay.

The other question, and I think this came up last time, was in terms of the CK drawing. Could you go over the protocol for CK drawing, and, again, since this is a U.S. protocol, many of the patients I'm sure were discharged before 24 hours, and so was

the infusion stopped and then the patient was immediately discharged, or did they have some post-infusion draw in all patients?

DOCTOR TCHENG: The protocol specified that serial CKMBs would be drawn at six, 12 and 24 hours, if I'm not mistaken. The infusions were continued for 20 to 24 hours. The patients were, as you have alluded to, ambulated frequently almost immediately after the termination of the infusion and then discharged home. Generally, the timing of the last CK draw was at the time that the infusion was discontinued, so, no, there was not another CKMB assay obtained prior to discharge after the infusion was terminated, in most cases.

CHAIRPERSON PARKER: JoAnn I think was first.

DOCTOR LINDENFELD: I just had a question. I know we talked about this last February, but just in a review by Doctor Topol in circulation last December, it states that the IMPACT study was not statistically significant at 30 days, could you just clear up that discrepancy for me?

DOCTOR TCHENG: I would beg to differ with that particular comment. In fact, Doctor Topol is here, if he would like to address it specifically. The

statistically significant result was achieved in the 135 and .5 arm, as specified in the protocol, a p value of .035 after adjustment for interim looks. The protocol specified value of .035 was an intention to treat analysis, and, in fact, as communicated with FDA by separate letter, the form of the analysis was a randomized as-treated patient analysis, that is, the patients were analyzed with treatment as they were randomized and, indeed, in the 135 and .5 group we did achieve statistical significance in a clinically relevant composite of death, myocardial infarction and urgent intervention.

Doctor Topol, would you --

CHAIRPERSON PARKER: Hold on this for a moment, because we may, in fact, want to ask Eric to comment on it, but probably a good idea to elucidate the issues first.

Lem?

DOCTOR MOYÉ: Yes, just to follow up on that. I mean, I appreciate the fact that you report a p value of .035, yet, in a manuscript that Doctor Topol wrote he reports the results were not significant.

In addition, the FDA reviewer, the stat reviewer, reports a p value of 0.041, which is greater

than 0.035. So, if there's a simple clarification, I sure would appreciate hearing it.

DOCTOR TCHENG: Perhaps, I can call on Kerry Lee to discuss the specifics of the statistical analyses.

DOCTOR LEE: Thank you.

I'm Kerry Lee from Duke University, and just a point of clarification with regard to the distinction between the .035 reported for the primary results of the IMPACT II study and the statistical reviewer's results. His results were actually based on using the so-called exact methods, they were actually computed in a slightly different fashion. The p value that was reported for the study was actually based on an ordinary Pearson's Chi Square statistic, which was the intent at the time the protocol was being written.

Our feeling was that with 4,000 patients the properties of the standard Chi Square test would be adequate to reflect the differences between the treatments being studied in this trial.

Whereas, the statistical reviewer for the FDA computed his p value using exact -- so-called exact methods, which does give a bit more of a conservative p value typically.

CHAIRPERSON PARKER: Well, can we hear from the FDA, do they accept the findings of IMPACT as being positive?

DOCTOR MOYÉ: Well, can we hear from the FDA, do they accept the findings of IMPACT as being positive?

CHAIRPERSON PARKER: Well, again, let's get into the general discussion of the issues first. I think that -- I guess I'm a little bit confused, and I apologize if this is reiterative from a year ago, but in the FDA review that this committee received this time the committee reviewer questioned whether an alpha of .05 had been adequately preserved if given a prespecified p value of .035, that p value of .035 was supposed to be corrected, not only for interim looks, but if I understand it, Kerry, tell me if I'm wrong, also for the multiple comparisons that could be made amongst the three treatments.

DOCTOR MOYÉ: Well, I guess my sense was there was a concern as to whether the 0.035, whether per comparison test really preserved an overall alpha of .05, and so that was what I thought the issue was.

I'm a little concerned now because there seems to be some discrepancy, which you have helped me clear up, as far as the FDA and your own analyses. I

am concerned that the manuscript that's appeared, though, also seems to support what the FDA claims, what the FDA stat reviewer claims, and that is the findings were not significant.

CHAIRPERSON PARKER: Let me just outline what the FDA review has stated. You probably have seen the FDA review, but from a public point of view to elucidate, and, Lem, correct me if quoting this incorrectly, although the protocol said that the final p value would be .035, the FDA review said that that did not preserve an overall experiment-wide alpha of .05, but that the experiment-wide alpha that would result from a p value of .035 was really .067, that is, it did not preserve the experiment-wide alpha of .05. Is that what you --

DOCTOR MOYÉ: No. For me, that's kind of a separate issue. I mean, if the investigator said .035 in the beginning, and it led to an overall alpha of .067, that's what they said in the beginning, and that's what I think they should be held to.

My concern is that the actual analysis the FDA claims did not come in at .035.

CHAIRPERSON PARKER: But, Lem, I'm sorry, I'm confused, because the investigator said that it was .035.

DOCTOR MOYÉ: Right.

CHAIRPERSON PARKER: But, it did not preserve the experiment-wide alpha of .05, because the investigator said so you would hold them to it even though it was incorrect?

DOCTOR MOYÉ: No. Well, I don't know that the statement about .035, as a prespecified per comparison, I mean, that's not correct or incorrect, that's what they said they wanted to be held to.

Now, it turns out the overall alpha for the entire primary endpoint comparison is 0.067, and that's kind of a discovery that occurred well after the trial was underway. There were concerns about whether the incorporation of the dependency between the comparisons was appropriate, but the fact of the matter is, the investigator said in the beginning .035, and I, speaking personally, I, for one, am comfortable with that decision.

What I'm not comfortable with, and what I'm asking for clarification on, is given that we accept the .035 prespecified alpha level, did they, in fact, attain that, and the investigators say that they did, and the FDA says they did not, and we have a manuscript that says they did not. So, that's my concern. I accept the .035 as a prespecified level,

my concern is whether they, in fact, met that.

CHAIRPERSON PARKER: Yes, Kerry, hold on a second, because you need to know which question you are responding to, and we're still trying to figure out what that question is.

Ray?

DOCTOR LIPICKY: I'm not sure I really know what to say, but --

CHAIRPERSON PARKER: That would be a first.

DOCTOR LIPICKY: -- but it's clear that taking the results of the trial and applying two different statistical methods to calculating a p value led to different numbers, neither number being spectacular, but both numbers being less than .1. Okay.

The second part of the same thing is that an overall alpha level of .067 and .5 in my estimation, and only my estimation, is sort of the same, and I don't think it would be profitable, or I don't think it is profitable, to try to make the results of the trial into a binary thing.

The question is, to what degree do the results of that trial support an effect. The conclusion that was arrived at last February was, not enough to draw a conclusion from that single trial,

and I really don't think it would be profitable to make a decision as to whether or not one should put the check mark in the no box or the yes box.

CHAIRPERSON PARKER: I think that the reason that we are going through the process is not because there is a major difference to be made between .05 and .067, or .035 and .041, but because there appears to be a difference, as JoAnn elucidated, in terms of how the investigators describe this trial in the literature and how the company is describing this trial to the committee. That distinction may be a very small distinction, but it is worthy of elucidation.

DOCTOR LIPICKY: But, the distinction you are worried about is the binary nature of the interpretation of the trial, not the persuasiveness of the trial with respect to whether or not something is found. The only thing you are deciding is whether the binary nature is important or not, or is binary or not binary, and how people arrived at their decision of yes or no, and that's okay. I'm not arguing that, but that is what you are pursuing.

CHAIRPERSON PARKER: Kerry, you may not know what we are asking, but I think you have an opportunity to respond.

DOCTOR LEE: Thank you very much.

There are two issues that have been raised here. Let me comment just briefly on both of those issues, if you wish.

The first is the issue about the discrepancy between the FDA statistical reviewer's results and what the IMPACT investigators reported. And, with respect to that, I would simply comment that there are multiple ways of performing these treatment comparisons from a statistical point of view. We could have used a log rank test, which actually produces a slightly smaller p value than .035, we could have used what we did use, namely, a convention Chi Square test for this binary endpoint, that's what produced the .035. There is the approach, which as implemented in software that's now readily available, the Stat Exact Software, which is what the FDA reviewer used, which produced this .041 p value, all of those are very, very close, and it depends on the selection of the particular statistical method as to which one one selects. We chose one particular method and that's what we've stuck by, maintained and reported consistently.

DOCTOR LIPICKY: That was your protocol specified method?

DOCTOR LEE: That was, yes.

DOCTOR LIPICKY: It was not something you dreamed up afterwards, but the FDA statistician dreamed up his test afterwards?

DOCTOR LEE: I think, Ray, one of the problems is that it may not have been as clearly documented in the original protocol as would have been desirable, so that there was absolutely no confusion, but this was our intent from the very beginning and that's what we've maintained.

DOCTOR LIPICKY: I think to be fair there is the protocol specified a comparison of proportions, as opposed to a time to first event analysis, but did not specify the precise test that would be used to perform a comparison of proportions, is that correct?

DOCTOR LEE: That is correct, yes.

CHAIRPERSON PARKER: Okay.

DOCTOR MOYÉ: I'd just appreciate some comment then about the manuscript. It's clear to me the issue between the .035 and .041, and I consider that resolved. I wonder if somebody could then comment about the manuscript, which says that the findings were not significant.

DOCTOR TCHENG: I would like to first comment about the publication of the primary results

of the IMPACT II trial, which actually appeared in the Lancet this spring, with a number of my colleagues here as co-authors. In that manuscript are actually presented the two different analyses that were performed in support of the IMPACT II trial results. Those are a standard intention to treat or an as randomized type of analysis, which I believe is what you are referring to. Our calculation was that the p value for that was .063.

The second analysis, which is provided in the manuscript at the same time, is this treated as randomized, or randomized as treated analysis, or as we are presenting here, the actual analysis that was prespecified with FDA that would be the primary analysis for support of Integrilin for approval, and that is where the value of .035 was attained.

That is what we were using, that is what we had intended to use as our specific analysis. However, if you would turn again back to the original Lancet manuscript there are two different types of analyses provided in the interest of providing the entire picture. The intention to treat, or classic intention to treat analysis, that is, an as randomized or as randomization allocation occurred, and then the treated patient analysis, which does not include the

139 patients who never underwent treatment with study drug, that particular analysis is provided to ascertain the best estimate of the true biological effect, the clinical efficacy and the safety issues of treatment with Integrilin.

CHAIRPERSON PARKER: Lem, could you comment on the idea that we see occasionally, that there are a certain number of patients randomized as before an intervention is to be performed, but the intervention is not performed in some of them, and the analysis is done only in the patients who had the intervention, but not in all the patients who are randomized. The difference in this case is 139 patients, and what are the pros and cons of doing an all-randomized analysis or as, I guess, the term that's being used here is, randomized as-treated analysis?

DOCTOR MOYÉ: The strength of using the analysis, the all randomized, or the intention to treat, is that patients are treated regardless of any other characteristic about them, and they are analyzed as though they were treated, regardless of any other characteristic.

Your attribution of effect is very clear and direct, because the only difference between patients who receive therapy and those who didn't is

just the therapy itself. Once you begin to peel that back, once you begin to allow patients not be treated for a variety of reasons, which may appear harmless and patternless at first, there, nevertheless, may be some underlying pattern which makes the attribution of effect very difficult.

The down side of the intention to treat analysis is that it tends to be less powerful, because you are including in the intervention group patients who didn't see the intervention, so, therefore, their history will be much like the placebo, a placebo control trial, like placebo patients, and you'll wind up reducing the impact of the intervention as a mean in the entire intervention group. So, you wind up reducing the efficacy and reducing the power.

CHAIRPERSON PARKER: Marv?

DOCTOR KONSTAM: Doctor Tcheng, you just mentioned that it was prespecified with the FDA, that the as-treated analysis would be the principal analysis, do I have that right? Could you just expand on that a little bit to the degree that that was really prespecified before the analysis was performed?

DOCTOR TCHENG: From the very beginning, our intent had been to perform an intention to treat analysis, and the principal investigators do consider

the treated as randomized analysis as a form of intention to treat analysis.

The answer to your question is, is that we had indicated in the protocol an intention to treat analysis, a subsequent letter was sent to FDA indicating specifically what that definition would be, and that was the randomized as treated analysis.

I believe Doctor Fleming, Tom Fleming, would also like to shed some light onto the course of events and his thoughts behind this issue.

DOCTOR FLEMING: Thanks.

Tom Fleming, Chair of Biostatistics, University of Washington. A few issues have come up here that I might like to address from a statistical perspective. The issue here of intention to treat is an important one, and it's critical to follow intention to treat to maintain the integrity of randomization. It's important, though, of course, to distinguish as treated versus treated as randomized,

Specifically, what the sponsor is advocating here is an analysis, not as treated, but as randomized, but not including those patients who were never treated initially.

In essence, it's critical to include all patients who are randomized in the analysis, in

essence, to preserve the integrity of randomization. If in any way the effective treatment or the knowledge of treatment could induce bias then excluding patients is something to avoid.

From my perspective, the only situation that's appropriate to alter an approach of using all randomized patients is in a blinded trial, where you exclude only those patients who aren't treated. In a blinded trial, we are excluding only those patients who aren't treated, it's not possible that the effect of treatment or the knowledge of treatment could be impacting the exclusions. So, there is no risk of bias in an analysis that is including everybody except for those people who are never treated, so long as that study is blinded. I think that's an important issue here.

Another issue that's come up is the distinction between, when you are comparing proportions, the distinction between the Fisher's Exact Test and the Pearson Chi Square. Actually, it's my understanding the protocol did state that they would be using a convention Chi Square. Both of these methods are appropriate. Often, we are a little bit misled, though, when we think of the Fisher's Exact Test, that's exact, right? Well, in essence, the

Exact Test is conditioning on both margins. It's not just conditioning on the number of people that are in the two regimens, it's conditioning on the number of successes. That second margin conditioning adds more discreetness and causes your p values to be higher, and, basically, it's causing unnecessary conservatism. Both the Fisher's Exact Test and the Pearson Chi Square are valid, meaning that if there's no effect they both preserve the type 1 error the size of the test. The Fisher's Exact Test is unnecessarily conservative, and so the Pearson Chi Square is, in fact, the most efficient valid approach, and that's what the sponsor used.

CHAIRPERSON PARKER: Tom, could you comment on the appropriateness of designating .035 for the analysis of each treatment arm to placebo, given the multiplicity of analyses and comparisons?

DOCTOR FLEMING: I'd love to, Milt.

You were at the Duke conference two months ago, as were several, this is a very important issue. Clearly, when you design a trial, it's extraordinarily important to preserve the error rates. It's important to avoid excess false positive conclusions due to the multiplicity of testing.

Multiplicity of testing arises in a lot of

ways. You can have multiple endpoints, you can have multiple test statistics for those endpoints, you can have multiple testing over time, and we adjust for all of those and we should.

Where there's a lot of confusion is, do you adjust for multiple treatment arms in the same trial, and I don't think there's any -- and, as in many discussions that we've had, there's no clear-cut consensus about that.

Is it important to preserve the error rate in the experiment or in the comparison? My personal view is, statistics can be of great assistance to us, but we've got to use our common sense and think about what the data are telling us when we apply statistics.

So, specifically, if you just look at the low dose Integrilin versus control, the p value is .035, and that's, essentially, as Lem has been talking about, on the guide as to what the protocol said, and the sponsor is being very meticulous to try to follow what the protocol said, and that's fine.

My argument is, that's fine, but let's practically think about what's happening here. If this trial had only low dose against placebo, would we be going away now saying .035, we're fine, that's less than .05. We have an additional set of information

here, it's the high dose. Daniel showed the curves, look at those six-month curves on high dose and low dose, those are telling us you have the same basic effect.

Now, at 30 days it turned out that there was a blip, so low dose looked better than high dose, but if you look over the entire six months you've got the basic same effect, but the essence of my point is, if you only had the data on low dose versus control we'd be saying it's .035. We have additional data on high dose that's giving us a confirmation of the strength of evidence, and so the essential point that I would make is, we should be thinking about the totality of the results that we have here, Milt, and when you bring in the low dose and high dose experience that, in essence, in my view, strengthens the sense of treatment benefit here, rather than if we just had the low dose versus control.

CHAIRPERSON PARKER: Is there any validity to doing a post hoc analysis, where one combines the two active arms compared to placebo?

DOCTOR FLEMING: Is there validity to it? It's post hoc, as you say, I think there is supportive validity to a lot of kinds of ways that we would try to explore strength of evidence, and so, it's

certainly a relevant supportive analysis.

But, it's ad hoc, as you say, and it's supportive.

CHAIRPERSON PARKER: Oh, I'm sorry, JoAnn?

DOCTOR LINDENFELD: I understand the point you made about common sense, but another common sense viewpoint might be that if the high dose were really supportive it would be significant.

DOCTOR FLEMING: Certainly the strongest case you would have in a clinical trial for strength of evidence would be if you had two doses against a control and they were both significant.

Obviously, in many instances, often because of sample size and power, it's not always that clear cut, and so we have to get into the issues of really bringing in judgment in interpreting information, and, in essence, that's where we are. It would have been a stronger case had the high dose regimen also been statistically significant. What certainly is, as I look at these data, compelling is that, I look at the data over the entire time frame and see a very consistent level of benefit from the low dose and high dose, certainly when you look over the entire six-month time frame, and in my view the data on high dose strengthen -- now, it's your judgment, do these data

adequately lead you to conclude it's a positive study, my view is the data on high dose strengthen my inference on low dose efficacy because I'm seeing the same level of benefit from a qualitative perspective.

CHAIRPERSON PARKER: Let's see, let's take this gentleman, please identify yourself.

DOCTOR SANKOH: A.J. Sankoh, a statistician.

I think there are three issues that have been raised that I want to address, I want to start with the .041 and .035 issue. I think if you can go back to the protocol, the protocol did actually say that they will be comparing proportions between the two groups. My interpretation of that is simply two ways. One, you want to know the clinical difference, numerical clinical difference, and how you can also see that with a statistical p value, so the p value they gave you there are on different proportions, you are not simply Chi Square, or you are not even Fisher Exact, as they are assuming, they are not Fisher Exact, these are based on difference on proportions. The difference comes in, basically, in this particular kind of test, when the proportions or the rates are very low, these tests to be a little bit more conservative than the Chi Square of the odds ratio.

When the rates are okay, I mean, acceptable, this test should give you the same, either use exact or asymptotic, so the difference you see in there is basically based on this type of method that I used. Okay. That's the first point there. So, they are not actually based on Fisher's Exact, as they are saying.

The number two, the difference between intend to treat and as treated, I don't understand what is randomized as treated, what it means, and I don't recall if I saw that, because this thing was reviewed about a year ago. I don't recall if I saw that there, but my understanding of intent to treat is all randomized patients, and as treated only those patients who received the intervention.

Now, if we are comparing a treatment to an active control, I can understand the idea of saying that you want to compare those patients who received the intervention only, I can buy that treatment if you give me only those who are treated. But, here we are comparing to no treatment, which is supposed to be placebo. For you to maintain the balance, which was created by the randomization, I think we usually provide the intent to treat data set for that type of analysis. That is where the difference comes in.

The number three case that I want to address, what do I say, Doctor Fleming was just talking about -- it's just skipped my mind, what was the last issue?

DOCTOR FLEMING: Should I address the first two while you think of the third?

DOCTOR MOYÉ: Was it multiple comparisons?

DOCTOR SANKOH: Yes, multiple comparisons, yes. Okay. The original protocol did actually specify that they were going to use a Bonferoni adjustment procedure, okay, that of .07 for the three comparisons, yes, .017, thank you. That was later altered to a .035, actually, I did ask several questions how the .035 was arrived at. I did not get a response.

Using methods that are in the literature, I came to the conclusion that they could have come from two methods, either the Tuki method or the Dubay imatage method, but those methods, based on a paper that was published in the Stat in Medicine, those methods are known to be very liberal. They inflict a type 1 error. So, if you look in the review, I did some simulation to show how the type 1 error will be inflated by using those particular methods. Okay.

CHAIRPERSON PARKER: Okay.

Tom, let me just try to focus this, because some of these issues are so generic that one could have another full day conference on this and may or may not make any progress, but I just wanted to make sure that we focus on one thing, and then there are some other comments from the committee, and then we probably need to move on.

Your argument that it is where you have two doses of active therapy versus placebo, and, therefore, there is no need to adjust for the multiplicity of arms because it would be as if one did, say, two trials with a common placebo, I think that would be a way of saying it, and, therefore, one could compare reasonably speaking each arm to placebo at .05. That's the argument that you would be making.

DOCTOR FLEMING: Not quite so liberal as the way you've described it. We do have to take into account all the data, it's all there, it's all real, it all matters.

The issue is, how do we summarize strength of evidence, what is, from my perspective, you have two regimens being compared to a common placebo. Now, the fact that there's a common placebo makes the results correlated when you look at the global results, but when you look individually at strength of

evidence, each of these comparisons can be compared to placebo at a one-sided .025, and you would get a sense of whether individually there is strength of evidence to establish according to our traditions for strength of evidence benefit.

That doesn't mean you ignore the fact that you have the other arm, it's the point, when I sit on an advisory committee that's when I want to see all the data, and if I see a result on low dose versus control and it's less than .05 two sided, less than .025 one sided, I also want to know what all the rest of the data tells me, and is this giving me a consistent signal. And, if I have other data, and it's telling me the same signal, it's strengthening the case that I have. If, on the other hand, the high dose showed harm, then it would be weakening and I wouldn't consider this a positive study if I were here on the committee, if I had an .020 and a high dose that showed harm, unless I had a heck of a good understanding for why there was such an enormous reverse dose response, so I'm arguing, you should look at all the data, you should factor it all in, but I think Ray's argument hits the nail on the head.

We may quibble about .026, .035, .030, those are essentially the same strength of evidence.

We've got to then think about the totality of the data and do these in a group, give us enough convincing evidence that this is benefit. That's what I would try to do on the committee.

CHAIRPERSON PARKER: I would only say that, just for the record, the philosophy, the philosophical position that one need not adjust for the multiplicity of internal comparisons was not the position that the investigators or the company took when they designed the protocol. I understand the argument, but that's not the position they took. They took a position of a full Bonferoni correction, with a p value of .017, and then subsequently modified it and presented a p value of .035, although it's not clear how they got that p value --

DOCTOR FLEMING: Right.

CHAIRPERSON PARKER: -- but they did take the philosophical position that a correction was needed, as opposed to a correction was not needed.

DOCTOR FLEMING: Indeed, they did in the attempt to be what I would call conservative, took the approach of saying, we will adjust, they originally put forward Bonferoni, then they stepped back and thought about it and said, there's correlation here, Bonferoni is overly conservative, and then were trying

to come forward with an adjustment that would account for that correlation.

So, indeed, to their credit, they are trying to do an adjustment for multiple arms, I'm trying to, in a way that's not driven by the study at all, but by a general principle, charging that we should be thinking about data in the totality, and the two doses are there, they are both important, they are both giving a signal, we need to look at what the totality of those two doses tell us in Integrilin as we are asking or answering the question, is there benefit.

Can I just very, very quickly, because I know we want to keep this focus and discussion short, very important issues are being raised here on the intention to treat and on Pearson Chi Square, Fisher's Exact, let me just quickly mention, back in 1978, Joe Burkson did an extensive study that shows exactly, as you say, in small samples both of these approaches are conservative, which gives us a good sense here. The true type 1 error rate, with either of these approaches, is below the nominal. It's just that the Fisher's is unnecessarily conservative, it's even more conservative because of the artificial discreetness imposed by the conditioning on both

margins.

Second point, I couldn't agree and encourage more that we go for intention to treat because that maintains the integrity of randomization, and I've always advocated, the only exception to that is when we are confident that any patients that are excluded cannot be excluded in any way that's either due to the treatment effect itself or the knowledge of the treatment, and the only circumstance I'm aware of that satisfies that is people in a blinded trial who have not had intervention, and that's not an as treatment analysis, that's treated as randomized. So, the only exception I could ever justify to intention to treat is in a blinded trial where patients had not received any treatment, because those people who are being eliminated aren't inducing bias because the treatment effect, nor the knowledge of the treatment assignment, could be impacting their exclusion.

CHAIRPERSON PARKER: Tom, it's always hard to know that there is no bias under those circumstances, because in every trial, where there are going to be some people who don't get the assigned therapy, you don't know that there isn't a bias.

DOCTOR FLEMING: The only bias that you could argue, though, in this case, Milt, would be if,

in fact, those patients did figure out their assignment before they started the treatment, then I would accept what you are saying as correct.

CHAIRPERSON PARKER: Yes.

Kerry, hold on one second, but stand by.

Dan?

DOCTOR RODEN: Thank you for allowing me to interject into this dialogue, Milton.

I have a question about the non-treated but randomized patients. There are only 139 of them, it would reassure me if I could see data on balance among baseline characteristics in that group and their outcome compared to others.

I'm going to pinch myself and I'm going to hope that I wake up from this bad dream.

DOCTOR DiMARCO: Dan, I just did the subtraction, it looked like there were two events, either death or MI, in the placebo group, six in the low dose, and four in the high dose, and adding those numbers is what converts it from, you know, the p of .035 to .067, to .063, or whatever it is, and it looks like the sponsor either got lucky or --

DOCTOR TCHENG: If we can turn off -- I'm sorry --

DOCTOR DiMARCO: And then, you know, I just

can't, looking at your Table 57, I really don't -- you know, I don't see in those indications for why the study was not administered, why they'd have somewhat a higher event rate.

DOCTOR TCHENG: Let me go through some data that will hopefully shed light on these issues. If we can have the main slides off and the back-up slides on, slide 327. Slide 327 will show you the patient enrollment in IMPACT II, the all patients randomized or, perhaps, a classic term would be intention to treat, if we can have the slide on. Thank you.

The top line, if I get this laser pointed, the top line is all patients randomized, you can see the total here is 4,010. This is the description of the patients, or these are the numbers for the patients where we are doing our primary analysis, the treated as randomized group, 1,285, 1,300, 1,286, the first thing you will notice is that the numbers are reasonably well balanced.

I might remind the committee that the IMPACT II trial was designed to be grafted onto clinical practice, so the randomization allocation occurred several hours before bringing the patient to the cath lab, that is before really the decision to perform intervention was actually made.

The patients who were randomized but not treated, for the large part, were patients who ended up not having a coronary intervention, that is, they were brought to the cath lab, or not even brought to the cath lab, and the decision was made not to perform the intervention.

If we can have slide 333.

DOCTOR KONSTAM: Could I just stop -- I'm just making sure I absolutely understand that point.

DOCTOR TCHENG: Yes.

DOCTOR KONSTAM: So, these were patients who did not even receive a coronary intervention, it's not that they received a coronary intervention but did not receive the drug.

DOCTOR TCHENG: No, that is not correct. We'll go through this slide, but if you received any study drug at all you were included in the all patients treated. There was an overlap of a small group of patients who did not receive intervention, who did not receive study drug, but there were also patients who did not receive study drug at all because the --

DOCTOR KONSTAM: That's -- I'm asking --

DOCTOR TCHENG: I'm sorry.

DOCTOR KONSTAM: -- the 139, did they

include patients who did undergo coronary intervention, but did not receive study drug?

DOCTOR TCHENG: Yes, it was a handful of patients.

DOCTOR KONSTAM: What constitutes a handful, just out of curiosity?

DOCTOR TCHENG: Perhaps, a dozen, something like that. And, the decision was made by the investigator, because of laboratory abnormality or something that was provided to the physician, to the investigator, after the randomization allocation that would indicate that it would be inappropriate to continue the patient in the study.

DOCTOR KONSTAM: Okay, but the vast majority, in fact, did not receive a coronary intervention at all, something like 125 of them or so did not receive any coronary intervention.

DOCTOR TCHENG: Yes. If we can go to slide 333, that actually delineates the reasons for no treatment. Again, randomized but no study drug was administered, here are the numbers 43, 49 and 47, as a contraindication to treatment, at least felt by the principal investigator, this is the group of patients who did not receive an angioplasty, that is, they were brought to the cath lab, had a cardiac catheterization

performed, and then the decision was made, because there was either no lesion or a lesion that couldn't be done, no angioplasty was performed, you can see here this is actually a patient who came in with thrombocytopenia, M.D. decision, that is, patient went for bypass surgery, you can see the breakdown here, inclusion/exclusion criteria were met -- excuse me, were not met post hoc, the numbers are here, consent was drawn, et cetera.

I think that the most important concept from this slide is that you can see balance among the groups for the reasons indicating that, as Doctor Fleming has alluded to, there was no knowledge of either the randomization and also no treatment with study drug as a reason for being analyzed in the randomized as allocated group.

CHAIRPERSON PARKER: What were the outcomes in the 12 patients who got an angioplasty and didn't get drug?

DOCTOR TCHENG: I do not have that data with me. We could -- I don't have that information.

CHAIRPERSON PARKER: Ray --

DOCTOR RODEN: You can't tell me what happened to these 139?

DOCTOR TCHENG: What I can -- some people

say they should be included in the total analysis, some people say they shouldn't, so it seems to me that it would be very, very useful for us to know what happened to these patients and how many of them met a primary endpoint.

DOCTOR DiMARCO: Well, it's two, six and four, no, that's death or MI, that's their primary endpoint at 30 days, is that right? That's what it says in the manuscript.

DOCTOR TCHENG: If we can go to slide 354, please, you are correct, you'll see what the difference in terms of the statistics are here. The randomized group is in the beige and the treated as randomized group is in the green. As you can see in the placebo, there was a few more patients who had events, and you can see also the effect on both of the treatment groups. It added an event or two in the placebo group, subtracted one in this group, and added one or two in this group. So, that's the breakdown of how the events happened, in terms of their composite endpoint at 30 days.

CHAIRPERSON PARKER: Let me simply, I think the committee has a general discomfort with exclusion of patients after randomization, particularly, by the way, in the case where they actually underwent the

indicated procedure, and I don't want anyone in the audience to get the impression that we think that exclusion of patients after randomization is a good policy to follow. It seems as if the investigators would agree with that statement.

DOCTOR TCHENG: We do.

CHAIRPERSON PARKER: Since the manuscript that presented the results actually presented what I assume was your preferred analysis, which was your all randomized patient analysis.

DOCTOR TCHENG: We provided both analyses in the manuscript, that's correct.

CHAIRPERSON PARKER: Right, okay.

Before going further --

DOCTOR RODEN: Can I just clarify one issue?

CHAIRPERSON PARKER: Sure.

DOCTOR RODEN: And, that is, this is a prespecified analysis?

DOCTOR TCHENG: Yes, that is correct.

DOCTOR RODEN: And, when was that analysis prespecified? I don't think I saw it in the protocol.

DOCTOR TCHENG: It was specified in the form of a letter prior to unblinding. We had no knowledge of the outcomes of the trial when we were

specifying --

DOCTOR RODEN: I see. So, the trial was complete but the study hadn't yet been unblinded.

DOCTOR TCHENG: That's correct, yes.

CHAIRPERSON PARKER: I see. So this letter actually was sent in after the trial was finished.

DOCTOR TCHENG: The protocol specified that we were to perform an intention to treat analysis. We had a number of discussions as to what form that intention to treat analysis would hold. We were anticipating some drop out, but we did not know how many, and, in fact, if you go through and compare this, for example, to the PURSUIT trial, which will come up, in the PURSUIT trial there were only 99 patients out of a trial sample sizes of more than double the IMPACT II trial that actually ended up in a comparable group, so this was a decision made after the trial was ongoing, after we realized the difficulty of the logistics of what we were trying to accomplish.

CHAIRPERSON PARKER: No, I understand, but the letter actually was sent before the blind was broken.

DOCTOR TCHENG: Before the blind was broken.

CHAIRPERSON PARKER: But, for all practical purposes, after the study had been completed.

DOCTOR TCHENG: Yes, that's correct.

CHAIRPERSON PARKER: Okay.

I'm sorry, the statistician, you do have an additional point?

DOCTOR SANKOH: Well, I just wanted to say, I don't recall that letter, I don't recall seeing anywhere. I recall the protocol saying intent to treat, okay, and my interpretation of intent to treat again is all randomized.

As I said, there are times when we tolerate all treated patients, but in most cases when that happens the two data sets would not give you a vast difference in terms of significance.

I cannot recall seeing that letter.

CHAIRPERSON PARKER: Okay.

I think we do need to move on, but let me just ask, the sponsor has said that death and MI are the real sort of hard endpoints here, and death and MI is, in fact, what was analyzed over six months of follow up. You showed the curves for six months, but you didn't show any p values, and it's not in your document. What were the p values for the treatment effect at six months for death and MI?

DOCTOR LIPICKY: Might I ask why you are asking? That's a retrospective analysis. It really doesn't lend itself to -- you can't interpret the p value in any conventional sense.

CHAIRPERSON PARKER: You cannot interpret the p value, but it's the hardest endpoints, it's the common endpoints between the two trials, and it's the longest follow up. It's a concept of reassurance.

DOCTOR LIPICKY: Yes, but how will you put those numbers -- what does the numerical value mean to you as opposed to looking at the survival curves, does that give you some more information?

CHAIRPERSON PARKER: Yes, I think that it would be different if it were .04. I don't think the issue is whether it's on .04 or .06, but I'd like to know how much of this might be -- whether the visual image may be due to the play of chance.

DOCTOR LIPICKY: Okay.

DOCTOR KITT: Unfortunately, we don't have the p value. You saw the Kaplan Meier curve, I can give you the exact numbers, if you'd like, of death and MI at six months.

CHAIRPERSON PARKER: Actually, I think we already have that number, but you have not actually calculated p value?

DOCTOR KITT: I'm sure we have, I don't have it right here at my finger tips. Someone is looking it up right now. I can give it to you in a minute.

CHAIRPERSON PARKER: Any other questions from the committee?

Okay, can you continue with the rest of the presentation?

DOCTOR GRETLER: Thank you.

Can I have my carousel back, please?

Well, I am now going to turn to the dose selection. In particular, I'm going to show you data that led us to adjust the dose upward for the PURSUIT study.

The dose selection for the IMPACT II study relied on ex vivo and in vitro aggregation studies, which had described the concentration response curve for eptifibatide as shown here.

It's important to note that these studies were all performed in sodium citrate. Sodium citrate is a calcium chelating anticoagulant that has traditionally been used in platelet studies.

However, as we continued to study the structure of the GP IIb/IIIa complex, and the pharmacology of its inhibition, we discovered that

calcium concentrations affect the pharmacology of eptifibatide. Specifically, what we found is that the very low calcium concentrations produced by sodium citrate in vitro enhances the effects of eptifibatide.

Let me show you what happened when we repeated these studies at physiologic calcium concentrations. This is the concentration response curve for eptifibatide at normal physiologic calcium concentrations shown in yellow here. This was achieved using another anticoagulant called PPACK, which does not affect calcium.

As you can see, there is a right shift of the concentration response curve, in other words, it takes higher concentrations of eptifibatide to inhibit platelets. The IC_{50}, the concentration necessary to inhibit platelet inhibition by 50 percent, we thought was around 140 nanomolar based on the early citrate studies. It was discovered that it was about four times higher, 570 nanomolar, at the more relevant physiologic calcium concentrations.

This in vitro difference has been confirmed in man as illustrated in these aggregation studies from a smaller PTCA study called PRIDE. Aggregation was measured over time after the administration of one of the IMPACT II regimens, the 135 bolus and the 0.75

infusion. The results at low calcium concentrations in vitro, in citrate shown in blue here, appear to show over 80 percent inhibition of platelet aggregation, but what happens at physiologic calcium concentrations in PPACK in the yellow curve. The targeted 80 percent inhibition is achieved, but only very briefly at the time of the 135 microgram per kilogram bolus.

What this all means is that there appear to be room for improving on the regimens used in IMPACT II, especially given the safety of eptifibatide in that study.

The rationale for the dose selection for PURSUIT was based on the following factors. First and foremost, the safety profile in IMPACT II, which was similar to eptifibatide and placebo, indicated no safety concerns. Second, the inhibitory dose of the IC_{50} for eptifibatide was higher than we thought when IMPACT II was designed, and third, the targeted 80 percent inhibition of platelet aggregation was not achieved throughout the infusion in IMPACT II.

Therefore, for the PURSUIT study we increased the bolus from 135 to 180 micrograms per kilogram, but, more importantly, we selected a two microgram per kilogram permitted infusion, a three to

four times higher infusion rate than what was used in IMPACT II. This new regimen was designed to reach and maintain a robust, at least 80 percent inhibition of platelet aggregation in the majority of patients.

The level of inhibition achieved in PURSUIT was, indeed, verified. These are data obtained at physiologic calcium concentrations in PPACK from a subset of PURSUIT patients who underwent aggregation studies. This was done in a 99 patient sub-study called PERIGEE.

The average inhibition was well over 80 percent, not only after the bolus, but essentially throughout the entire duration of drug administration. This sub-study, PERIGEE, also indicated that over 80 percent had platelet aggregation inhibited by at least 80 percent at steady state, and also receptor occupancy averaged over 80 percent.

These data indicate that the pharmacologic target in PURSUIT had, indeed, been achieved.

To summarize, there is a common pathophysiology in unstable angina, and non Q-wave myocardial infarction, and in the post angioplasty state, the conditions we studied in IMPACT II and PURSUIT.

The pharmacology of GP IIb/IIIa inhibitors

represent an excellent match for the pathophysiology of acute coronary syndromes.

The IMPACT II study has demonstrated efficacy and safety of eptifibatide in patients undergoing PTCA.

And lastly, new pharmacology studies have shown that the IMPACT II regimen did not maintain the expected level of platelet inhibition. With that incite, and given the excellent safety profile of eptifibatide in IMPACT II, the dosing regimen was increase for PURSUIT. This dose adjustment allowed us to reach our pharmacologic target in over 80 percent of the patients at the dose we are recommending for clinical use.

And now, I would like to introduce Doctor Robert Harrington from Duke University, who will discuss the results of the PURSUIT study.

CHAIRPERSON PARKER: Does the committee have any questions on the clinical pharmacology?

Dan, you didn't take your Dilantin today, but it has a lot of pharmacokinetics interactions.

Okay, please. Oh, JoAnn, I'm sorry, go ahead.

DOCTOR LINDENFELD: I just had a question on the FDA review, maybe I'm reading this incorrectly,

but it suggests that aggregation of five minutes, one hour and four hours are only about 50 percent. Let's see, maybe I'm reading, not the same study, but Mary Ann Gordon's review? Yes, page three of that, using PPACK as the anticoagulate, ADP and robust platelet aggregation at five minutes is 83 percent, but at one hour is 48 percent, four hours is 54 percent.

DOCTOR GRETLER: What dose was this?

DOCTOR LINDENFELD: Let's see, this is from PURSUIT.

DOCTOR LIPICKY: Where are you looking explicitly?

DOCTOR LINDENFELD: It would be page three of Mary Ann Gordon's review on the pharmacokinetics.

DOCTOR GRETLER: In the meantime, could I maybe have my slides back, fourth slide before the last one way at the end, it's the fourth to last slide. Yes.

These are the results from the PERIGEE study, which is the subset of patients in PURSUIT who underwent platelet aggregation studies. These are the only patients in PURSUIT who did undergo platelet aggregation studies, and these are the results obtained in PPACK, and so the results, the study states level of inhibition is about 90 percent.

DOCTOR LINDENFELD: Well, maybe we can get some confirmation, because I'm on page three, this says high dose Integrilin group only from the PERIGEE study.

DOCTOR GRETLER: If it says high dose, could it be the IMPACT II high dose?

DOCTOR LIPICKY: Mary Ann, do you recognize what's being discussed?

DOCTOR GORDON: It's really been a while, but if I recall correctly it was from PURSUIT, and you only use the one dose, one of the doses was dropped.

DOCTOR GRETLER: Yes, you are absolutely correct. As Doctor Harrington is going to explain, PURSUIT was started using two eptifibatide doses, a 180 bolus followed by a 1.3 microgram per kilogram infusion, and then the dose that -- the preferred dose that we continued all the way to the end, the two microgram per kilogram per minute.

However, by the time the PERIGEE study was started, we, essentially, had already dropped the lower dose.

DOCTOR GORDON: Correct, we had no information on the --

DOCTOR GRETLER: In fact, one patient, we had information on one patient at the low dose, so all

these data were obtained at the high dose, at the --

DOCTOR GORDON: And, you used the two anticoagulants -- you compared two anticoagulants and the two agonists in the PERIGEE.

DOCTOR GRETLER: Yes, we also looked at TRAP, and this is -- all the curves I showed you were ADP.

DOCTOR GORDON: Okay, well, I also looked at the TRAP as well in my --

DOCTOR GRETLER: Okay.

DOCTOR GORDON: -- is that what you are looking at, JoAnn?

DOCTOR LINDENFELD: Well, it's the --

DOCTOR LIPICKY: The perception is you are describing something different than what the sponsor is showing.

DOCTOR GORDON: Well, I showed all the data, meaning using the two anticoagulants, the PPACK, and then the sodium citrate, and also the two agonists, ADP and the TRAP.

DOCTOR LIPICKY: But, your words did not mean to differ from what is being presented now, or your words meant to differ?

DOCTOR GORDON: Well, I'm saying that there were four different results, four sets of results.

DOCTOR LIPICKY: Four different sets of results, of which only one is being shown.

DOCTOR GORDON: Yes, and I showed four, that's why my --

DOCTOR LINDENFELD: But, the point I'm trying to get at is, with the high dose Integrilin, the highest dose in any of these studies, that within the first 24 hours there was not 80 percent inhibition of platelet aggregation, except with the bolus, and then there's a drop and then it goes back up to 24 hours.

DOCTOR GORDON: Certainly with the TRAP agonists it was not.

DOCTOR HOMCY: Can I help?

DOCTOR GORDON: Sure.

DOCTOR HOMCY: Maybe I can help. The goal of the study was to get robust --

CHAIRPERSON PARKER: Identify yourself, please.

DOCTOR HOMCY: -- oh, I'm sorry, I'm Charles Homcy from COR Therapeutics. The goal of the study was to achieve more than 80 to 85 percent receptor occupancy, which was achieved with this dose, the 182.0, and when you achieve 80 percent receptor occupancy you come close to ablating ADP-induced

activation of platelets. So, in these studies, over 80 percent of the patients were inhibited more than 80 percent to the agonist, ADP, which is the typical agonist that is used in most trials of this class of agents.

There is another agonist called TRAP, which is thrombin, which is more potent, and higher levels of receptor occupancy are needed to block that agonist, but with this agonist, at these doses, with this anticoagulant, there was robust platelet aggregation inhibition at all time points, as you can see from this slide.

DOCTOR LINDENFELD: Well, that's different than what's in this review, though, within the first 24 hours. This suggests 50 percent.

DOCTOR HOMCY: Well, I don't know where that number is coming from, but this is the only data that exists.

DOCTOR LINDENFELD: I'm just saying that's different than this --

DOCTOR HOMCY: I think you are looking at TRAP, the agonist TRAP.

DOCTOR LINDENFELD: No, I'm looking at ADP, at least in the column -- maybe Mary Ann can clear this up for us, but at least in this first column it's

quite clearly ADP.

DOCTOR HOMCY: Well, I can't help to solve that.

DOCTOR LIPICKY: So what -- I'm still confused, do you, in fact, accuse the sponsor of saying the incorrect thing here in your review?

DOCTOR GORDON: No. I used the --

DOCTOR LIPICKY: Or, is your review not being interpreted properly by the questioner.

DOCTOR GORDON: -- I used the numbers that the sponsor had in their reviews.

DOCTOR LIPICKY: And, your graph looks like that?

DOCTOR GORDON: I have -- again, they looked at four different things, but --

DOCTOR LIPICKY: Well, does one of your things look like that?

DOCTOR GORDON: I used the bar graph.

DOCTOR LIPICKY: Yes, but it would look like that.

DOCTOR GORDON: Roughly, it looked like that. They did lose -- they lost after the bolus, they had high occupancy rate after the bolus, and then when they started the infusion it dropped dramatically.

DOCTOR LIPICKY: So, you did not mean to imply that this is an incorrect perspective.

DOCTOR GORDON: No, I did not mean to imply that.

DOCTOR LIPICKY: Does that help you?

DOCTOR LINDENFELD: Well, just the review here says that patients achieve greater than 80 percent inhibition of platelet aggregation during the bolus, this percent was not maintained at hours one and four of the constant infusion.

By 24 hours of the infusion, all patients with data had achieved the target inhibition of platelet aggregation.

DOCTOR GORDON: It dropped to about 48 percent when they started the infusion.

DOCTOR LINDENFELD: Forty-eight percent at one hour, right?

DOCTOR GORDON: Yes.

DOCTOR LINDENFELD: So, that means that --

DOCTOR LIPICKY: So, that does not look like that.

DOCTOR LINDENFELD: It does not look like that, at least my interpretation is.

DOCTOR HOMCY: I think I can clarify. I think now I understand what you are saying.

What's being said is that the -- this is the data from which her table was calculated, I think what she's calculating is the percentage of patients who are 80 percent at one hour. And so, what this graph says is that about 50 percent of the patients at one hour are at 80 percent platelet aggregation in the small study. At steady state, what Doctor Gretler said is also correct, so at the bolus you can see you are at about 90 percent at five minutes, it bounces up, but still the level of platelet aggregation in PPACK, the mean is 80 percent, but if you calculate the standard deviation from this, in terms of the patient population, about 50 percent of the patients are below and about 50 percent of the patients are slightly above. At four hours, that's improved, and at steady state 90 percent -- over 80 percent of the patients are 90 percent inhibited.

I hope that helps.

DOCTOR GRETLER: Right, in fact, at 24 hours there were 84 percent that were at least at 80 percent inhibited, at 48 hours and 72 hours the numbers get smaller, but 100 percent of the patients were above 80 percent.

CHAIRPERSON PARKER: Ileana?

DOCTOR PIÑA: Yes. My question is to back

you up for a few minutes. When you did your platelet aggregation at the end of your first trial, and you realized that the analysis of platelet aggregation with the citrate may not be as accurate as you would like it to be, or, perhaps, not as physiologic, you went back to the drawing board and recalculated a new dose.

What I'm seeing here is, this is the sub-study from the subsequent study, where you had already chosen a higher dose, in other words, in PURSUIT, did you do some interim studies to make sure that you chose a dose that adequately addressed this? In other words, how did you choose this dose? I saw how the curve moved to the right with the PPACK analysis, so you increased your bolus, how did you come to a higher infusion dose? What studies did you do? Am I clear in my question?

DOCTOR GRETLER: Yes, I believe I understand your question, and the answer is, we did not do any studies in man. The 182.0 regimen was the highest dose ever given to patients at the time we started the PURSUIT study, and it was derived based on the in vitro data that I showed you.

And, as I showed you, the bolus was increased only slightly, because we knew that the 135

microgram per kilogram bolus just barely reached the 80 percent target that we wanted, but we knew the infusion really fell short. So, the infusion rate was the one that was really increased.

DOCTOR PIÑA: So, your increase from an infusion of about three --

DOCTOR GRETLER: Yes.

DOCTOR PIÑA: -- to five was empiric in that sense.

DOCTOR GRETLER: Yes, it was based on in vitro data.

DOCTOR PIÑA: Did you have any data on bleeding complications at that infusion level from any of the previous data within the company?

DOCTOR GRETLER: No, we did not.

DOCTOR KITT: We did, on the other hand, recognize that we had not yet studied that dose in man, and we took this approach to go directly in the PURSUIT study to 182.0 based on the safety profile that we saw in IMPACT II. Doctor Gretler put up the instance of major bleeding, in which there is virtually no difference between the two groups in major bleeding. So, we felt as though, number one, we had a good safety profile as a foundation to move up. The second, as I believe you've seen in the review of

PURSUIT, is we inserted a safety review at 300 patients, recognizing that this was the first time we'd been up that high. And, the Data and Safety Monitoring Committee was charged with verifying that in this, so to speak, small group of patients, 300 patients, that the safety profile was, indeed, reasonable, and, once again, we inserted the 1.3 continuous infusion in PURSUIT just, again, because of a concern of safety.

But, the direct answer is, we did not have any data like this before PURSUIT started, however, we've calculated what the level of plasma concentration we needed in PURSUIT to achieve this level of platelet aggregation and, indeed, we are very pleased to see that we hit it.

CHAIRPERSON PARKER: Okay.

Can we pursue PURSUIT?

DOCTOR HARRINGTON: Thank you.

If I could have my first slide.

What I'd like to do over the next 20 minutes is to present to you the primary results of the PURSUIT trial, and I'd like to start with some background and rationale, some of the underpinnings of the trial as conceptualized by the investigators and by the Steering Committee.

To try to get at some of the issues of dose selection, and what the thinking was of the investigators as we designed the trial, we'll walk you through in some detail the study design and the thoughts of the Steering Committee at that particular time. We'll then share with you the primary efficacy and safety results, and try to provide some clinical perspectives in conclusion.

Unstable angina, as is no surprise to anyone on this committee, is clearly a global public health problem. It's been estimated that there are greater than a million patients presenting annually to both U.S. and European physicians with the problem of acute coronary syndromes without ST segment elevation.

One of the difficulties, both in diagnosing and in treating the population without ST segment elevation is the heterogeneity of the population. ST segment elevation acute coronary syndromes, by and large, are pretty simple both to diagnose and to treat. These patients are having acute myocardial infarction and they need reperfusion therapy.

The group of patients without ST segment elevation are a bit more heterogenous, and that is that in retrospect it might be discovered that that patient had, in fact, been having an MI, they may have

been found to have unstable angina, meaning a syndrome without myocardial necrosis or, in fact, a small minority of these patients may turn out to have non-cardiac chest pain.

In part, because of the heterogeneity of the population, there has been heterogeneity in treatment, in both medical strategies as well as invasive strategies utilizing cardiac catheterization and revascularization has been employed in the management of these patients.

Recognizing this, the Steering Committee at the time felt that there were limitations and problems with previous trials looking at new drug therapy or treatment strategies in the population of patients with unstable angina.

We felt that many trials focused on narrow populations, whereby it was testing a pathophysiologic proof of concept. In many of these trials, there was a mandated treatment strategy that included either an invasive approach, utilizing cardiac catheterization or vascularization, or a more medically-oriented approach, and it was felt that this forced clinicians to extrapolate the results from a narrow population to a broad clinical practice.

PURSUIT, therefore, was conceptualized and

designed as a large simple trial, to enroll a broad global population of patients into the trial. In a sense, this was an all comers trial. All treatment decisions, including any decision for cardiac catheterization and revascularization were solely left to the discretion of the treating investigator without any protocol mandates.

It was then felt by the investigative group that we would be able to examine a new therapy in a clinically-relevant population, and, in addition, gain incites into both the heterogeneity of patients in practice, as well as some sense of the outcome of patients in this very diverse group.

What you see here is the study design for the PURSUIT trial. Patients who had ischemic pain occurring at rest within the previous 24 hours were eligible for enrollment. They then also needed some sort of objective evidence of coronary disease. They needed to have either electrocardiographic changes, which would be suggestive of ischemia, ST segment depression, T-wave inversion, transient ST segment elevation or they needed at the time of enrollment to already have evidence of myocardial necrosis with the appearance of a positive CKMB fraction.

As I said, treatment decisions were left to

the discretion of the enrolling physician, and that included other medical therapies, like Aspirin and Heparin, though both were highly recommended.

Patients were then randomized initially in a three-way scheme to two doses of eptifibatide, a common bolus dose of 180 microgram per kilogram, followed by an infusion of either 1.3 or 2 micrograms per kilogram per minute. As has already been discussed by Doctor Gretler, with the laboratory findings that the 180 2.0 dose would probably provide high levels of platelet inhibition, this was the dose of interest to the investigators. Because, as has already been pointed out, these doses had not been studied in any broad sense in a patient population, we included a low dose group.

Now, as part of the charge of the trial, it was prespecified in the protocol for an independent Data Safety Monitoring Board to review the data at approximately 3,000 patients, at which time this independent Data Safety Monitoring Board would have access to the safety data of the trial, the bleeding, the strokes and the mortality. They would then, based upon this data, make a decision if the high dose group appeared to have an acceptable safety profile to discontinue enrollment into the lower dose group and

continue for the remainder of the trial in a two-arm fashion.

Both infusions were given up to the time of hospital discharge, again, in keeping with the clinically-based practice approach, or 72 hours, whichever came first.

Recognizing the benefits of antiplatelet therapy in the patients undergoing angioplasty, if an angioplasty was performed near the end of the 72-hour infusion, patients could get an additional 24 hours, up to a total of 96 hours.

As I've said, this prespecified review occurred at approximately 3,200 patients. The independent committee had access to the safety data, and they, in fact, selected the low dose group to drop. Enrollment in the trial continued throughout this period in terms of efficiency in the large trial design and from the site investigative point of view this was a completely seamless transition to two arms.

Exclusion criteria, in the trial of what one would expect of a novel antithrombotic, items to try to decrease the bleeding risk, including a history of recent bleeding, recent surgery, history of hemorrhagic stroke, a variety of laboratory findings which might predispose patients to bleeding risk.

On this slide you see both the efficacy and safety endpoints of the PURSUIT trial. The primary endpoint of the trial was the composite occurrence of death or myocardial infarction occurring at 30 days. Myocardial infarction, as the primary endpoint of the trial, was all to be adjudicated by an independent, blinded Clinical Events Committee, and we'll have more on this in the next slide.

There were a host of secondary endpoints, of which some I've included on this slide. We were interested in the early effects of the drug, remembering that the drug would be given for between 72 and 96 hours, and also at the seven-day period, which was felt to represent approximately the time that most of these patients would be going home from the hospital.

We were interested in the question of medical treatment versus PTCA treatment, and we were also interested at following these patients out to a more intermediate time point at six months.

Bleeding was carefully ascertained in the trial and two measures of bleeding were performed, the GUSTO scale, which depends upon an investigator-determined definition of bleeding, mainly based on transfusion requires and the presence or absence of

hemodynamic stability. The TIMI scale is basically a laboratory-derived definition of bleeding, and we'll show you both of these results as well.

Finally, strokes, particularly, intracranial hemorrhage, were all carefully reviewed by an independent events committee that included neurologists.

The clinical events process was to ensure that in this large trial that took place in over 27 countries that we had adequate systematic and standardized review of the suspected endpoints. All suspected endpoints were identified in a computerized algorithm of the database, looking at case report form variables, ancillary form variables, including rehospitalization forms, and data from an independent electrocardiographic core laboratory. If an event was suspected by the events by this review, and by the Events Committee process, source documentation would be collected.

There was then independent review by two cardiology fellows, looking at the details of the case. If the cardiology fellows agreed that an event had occurred, or had not occurred, the case was considered adjudicated and finished, with the exception that there was quality control done on

approximately ten percent of these agreement cases.

If there was disagreement, this went to a faculty review, whereby senior cardiologists would review the case in detail and arrive at a consensus decision as to whether or not an event had occurred.

The statistical assumptions behind the trial, based on results from previous trials, much smaller trials in this area, were that there would be an estimated placebo event rate, death and myocardial infarction composite occurring at 30 days of approximately eight to 8.5 percent. It was felt that approximately 9,400 patients would need to be enrolled into the two primary treatment comparisons to have 80 percent power to detect a 20 percent reduction in the primary endpoint. This translates to an absolute reduction of approximately 1.7 percent at an alpha level of .05.

DOCTOR MOYÉ: That's two tailed, right, or not?

DOCTOR HARRINGTON: That's correct.

DOCTOR MOYÉ: Two tailed?

DOCTOR HARRINGTON: Correct.

DOCTOR MOYÉ: Thank you.

DOCTOR HARRINGTON: Enrollment for this trial began late in 1995 and ended in mid-January,

1997, a total of almost 11,000 patients were enrolled in 27 countries in over 700 investigate sites around the world. On this slide, you see the representation of countries involved in the trial, and I'll point out that the highest enrollment country was the United States, counting for 4,000 of the almost 11,000 patients. The next largest region of the world was Western Europe, contributing another 4,000 patients, and then there was enrollment in Eastern Europe and Latin America.

What you will see from here on in, when I speak both to the baseline characteristics, some of the procedural details, as well as the efficacy and safety results, are the primary comparisons in the two treatment groups, the eptifibatide 180 and 2 dose, and the control group.

I've included only very few of the baseline characteristics. More details are in your briefing documents, but you can see that this is a pretty typical non-ST segment elevation population, with the median age in the mid 60s, approximately a third of the patients being female, the typical distribution of cardiovascular risk factors, and a fair amount of previous revascularization that had taken place in the population were 12 percent having previous CABG and

about ten percent having undergone previous angioplasty.

The great majority of these patients, over 90 percent, had some sort of electrocardiographic abnormality at the time of enrollment. These are not mutually exclusive, since a patient might have more than one type of EKG finding. The majority of the patients had either ST segment depression or T-wave inversion. About 14 percent of the patients had transient ST segment elevation as their entry criteria.

In retrospect, it was felt by ascertainment of the enzymes, and by review of the case report forms, that approximately 45 percent of the patients were determined to have been having a myocardial infarction at the time of enrollment.

What you see on this slide are the in-hospital cardiac procedures. About 60 percent of the patients underwent cardiac catheterization, with approximately a quarter undergoing some sort of percutaneous revascularization. Approximately half of those undergoing percutaneous revascularization had a stent implantation. About 14 to 15 percent of the patients underwent surgical revascularization during the initial hospitalization.

What you see on this slide is the primary endpoint of the trial. This is the composite of death and myocardial infarction with the myocardial infarctions adjudicated by the independent committee. You can see that here is a statistically significant reduction in the primary endpoint from 15.7 percent to 14.2, an absolute reduction of 1.5 percent. This effect is mainly driven by the reduction in myocardial infarction.

Looking at the time to event curves, you can see that there is early separation of the two groups, with maintenance of the benefit without deterioration in the absolute effect or accumulation in the absolute effect out to the 30-day measurement period. The p value here has been calculated using the log rank test.

Trying to get a sense of where the drug is exerting its biological effect, I'm showing you here the time to event curve blown up over the first seven days. What you can see is that there is separation of the curves that begins around the one-day period, the maximum benefit that's going to be achieved is achieved by about the three-day period, and that is completely maintained in terms of absolute benefit to seven days, where you can see the absolute difference

being approximately 1.6 percent.

Looking at the data in another way, with the odds ratio plots, with the prespecified secondary endpoint timing of 96 hours, seven days, and the primary endpoint at 30 days, again, a couple things here worth noting. The absolute benefit that's going to be seen is seen during the time of drug infusion or shortly thereafter, the end of 96 hours there's an absolute reduction in the endpoint of approximately 1.5 percent. That absolute difference is completely maintained to the end of the 30-day measurement period. As would be expected, as additional events are accumulated equally between the two groups, there's a relative decline in the relative treatment benefit.

The primary endpoint of the trial was the independently adjudicated CEC assessment of myocardial infarction combined with mortality. We also looked at the investigator's assessment of myocardial infarction as part of the composite, and what you see on this slide is the investigator's assessment of the composite endpoint at 30 days. You can see a couple of things, one of which is there's concordance of the findings with the central adjudicated committee in that there is a statistically significant reduction in

the endpoint, in this case on the magnitude of 1.9 to 2 absolute percentage points, again, mainly driven by the effect on myocardial infarction, and you can see that the overall numbers of events are lower, giving us a larger relative effect, though the absolute effect remains the same.

You can see in the time to event curves, using the investigator ascertained endpoint, again, early separation of the curves, complete maintenance of the absolute benefit out to 30 days.

A variety of subgroups were analyzed in the population looking at the treatment effect. I'm only going to show you a small handful of them here, the rest are in the briefing book. You can see that overall there is a nice consistency of the treatment effect in a variety of the subgroups that were looked at, with the exception of gender where the point estimate for the treatment effect in females favors placebo.

As stated in the beginning, this was a trial that took place in 27 countries and over 700 investigative sites. There were four distinct geographic regions that took place in the trial and managed by the two coordinating centers. Over 80 percent of the patients were enrolled in North America

and Western Europe.

Here you see the odds ratio plots with the point estimate, the size of the point estimate representative of the relative proportion of patients enrolled from that region. What we can see, as we've seen in some of the other large international trials, is that there is some geographic variability here that all point out that the wide confidence intervals in both Latin America and Eastern Europe likely representative of the smaller sample size from those regions. This is from the CEC adjudicated endpoint.

If we look at the investigator endpoint in the four regions, using the investigator-determined myocardial infarction, you can see on this slide, again, broad confidence intervals in Eastern Europe and Latin America, and the point estimates all favoring eptifibatide.

One of the question that might arise is, what kind of myocardial infarctions are actually being prevented in this trial by treatment with the antiplatelet agent. On this slide, you see an analysis looking at all of the myocardial infarctions identified, these are the events identified by the Clinical Events Committee, and then looking at the large infarctions, large infarctions being defined as

CKMB elevations greater than five times the upper limit of normal, as well as Q-wave infarctions. You can see that these large infarctions make up approximately a third, or a little more than a third, of the overall myocardial infarctions. There's a nice trend towards treatment benefit here, reducing the large infarctions from 5.4 to 4.5. You can see when you combine that with death the effect on the composite here.

If we look at the Q-wave infarctions, I think a couple of interesting things stick out here, one of which, as has been expected, the relative rate of Q-wave occurrence in this population is quite low. Nonetheless, there's a nice effect here on the Q-waves, reducing them from 1.7 to 1.1 percent.

The six-month data on this population has recently become available, and what we are going to share with you on the next two slides are the six-month mortality outcomes, as well as the six-month composite of death and myocardial infarction. In the time to event curve, you can see that there is no effect on mortality measured out to the end of the six-month observation period.

In measuring myocardial infarction beyond 30 days, we relied on the investigator-determined

infarction occurring between 30 days and 180 days as part of the endpoint. These events were all confirmed through ascertainment of hospital discharge records, but they were not independent adjudicated by a Clinical Events Committee. Therefore, on this slide I've included the myocardial infarctions through 180 days as assessed by the investigators to give some overall consistency.

You can see again the early separation of the curves with maintenance of the benefit, the absolute reduction at the end of six months to be 1.5 percent and the composite of death or MI, and you can see the p value here on the bottom part of the screen.

Well, safety is obviously an important part of the termination of a novel antithrombiotic, and what you see here is the stroke rates in the trial in the two treatment groups. All strokes, all suspected strokes, were independently adjudicated by this committee, that included representation from neurology. The overall total number of strokes is very similar, and importantly, there is no increase in the risk of primary hemorrhagic stroke.

With regard to bleeding, you see bleeding represented on this slide in two fashions, using the TIMI scale, as well as the GUSTO scale, and there is

an increase in bleeding whether measured by the TIMI scale, a laboratory-derived method of determining bleeding, or the GUSTO scale, based more on clinical characteristics, and there is an increase in bleeding comparing placebo to the antiplatelet agent.

As we try to get a sense of where this bleeding was occurring, we looked in the patients who had the most severe form of bleeding, the major bleeding, at where the bleeding was occurring. In the bleeding, from nine percent to almost 11 percent, the majority of those major bleeding events occurred in the patients undergoing surgical revascularization.

Importantly, there's no increased risk of bleeding in those patients undergoing bypass surgery who had received the antiplatelet agent.

In a similar fashion, we looked at that group of patients receiving PTCA, and there is a risk of bleeding that's increased with the antiplatelet agent, though the overall numbers here are quite small.

Looking at bleeding in yet another way, the transfusion, the way that the GUSTO scale is derived from the requirement of transfusion and whether or not it's associated with hemodynamic instability. What you can see on this slide is that there is an increase

in need for transfusion in the patients treated with the antiplatelet agent, and you can see that this occurs over all the number of units required by the particular patients.

Again, the same type of analysis that you saw two slides back, looking at where this bleeding occurred. The majority of bleeding and transfusion requirements in this population occurred in the group of patients undergoing surgical revascularization, and, importantly, there was no increase in the risk added by treatment with the antiplatelet agent.

Thrombocytopenia has certainly been a concern with this overall group of -- this class of drugs. In the protocol, the definition of thrombocytopenia was platelet count less than 100,000 occurring during the hospitalization or a decrease of greater than or equal to 50 percent from baseline. We also looked at more profound levels of thrombocytopenia of less than 50,000 nadir and less than 20,000 nadir counts. What you can see here is that the general level of thrombocytopenia, there is no increased risk with treatment with the antiplatelet agent, at the more severe levels of thrombocytopenia the overall numbers here are quite low, but there is an excess in the eptifibatide treated group, moving it

to less than 50,000 by an excess of seven as well as in less than 200,000 an excess of seven, moving from two cases out of 4,600 to nine cases out of the 4,600.

To put this in some sort of clinical perspective, what I've displayed on this slide is the events prevented per 1,000 patients treated, and if we look at the various time points and look at whether it's the CEC derived definition of the endpoint, the primary endpoint of the trial, or the investigator's determination, that there's roughly 15 events prevented per thousand patients treated at all of the time points.

So, in conclusion, PURSUIT is the largest trial of acute coronary syndromes without persistent ST segment elevation that has been performed to date. In the concept, as designed by the Steering Committee, we were able to enroll a global distribution of patients and to examine a global distribution of management strategies. There was a clinically relevant and a statistically significant reduction in the primary death/MI composite which was observed at all time points.

The greatest benefit of treatment was observed in North America. Importantly, and in distinction to other agents such as the thrombolytic

agents, there was no increased risk of hemorrhagic stroke, and the increased bleeding with eptifibatide mainly was that, was access related in the interventionally treated patients and manageable from a clinical point of view.

PURSUIT thus confirms the importance of platelet-dependent thrombosis in the adverse complications of the acute coronary syndromes, and eptifibatide reduced the irreversible clinical events of the composite of death and myocardial infarction with an acceptable safety profile.

Thank you.

I'd now like to introduce Doctor -- do you want me to hold on for questions?

CHAIRPERSON PARKER: I guess I wasn't quick enough there. I'd open it for general comments, starting with our primary reviewer, John DiMarco.

DOCTOR DiMARCO: Could you clarify for me the pattern of CK drawing, looking at the protocol it looked like eight and 16 hours after the start of the infusion were the only times that were prespecified, the other CKs, which accounted for a large number of your events, were sort of randomly drawn?

DOCTOR HARRINGTON: The trial was designed to mimic clinical practice, and so the enzymes that

were drawn were drawn at the invest -- what they did in standard clinical practice. So, we wanted the early enzymes to determine whether or not an event had occurred at the time of enrollment, so as not to be confused with an endpoint event, and so those were protocol mandated.

After that, this is a group of patients that typically would have enzymes drawn based upon the investigator's particular hospital, every eight hours for the first 24 hours, every 12 hours for 24, and then would be done with suspected ischemic events.

If you like, I can show you what kind of enzyme ascertainment we had for the population.

DOCTOR DiMARCO: I would like to see that if you have that.

DOCTOR HARRINGTON: Could we have the back-up slide 466? What you'll see is that because we were very aggressive about collecting enzymes, we actually had done a better job of this than we have done in previous trials in a similar population.

Many of you will be familiar with the GUSTO IIb trial, a trial of a thrombin inhibitor in this similar population. This is looking at the enzymes CK and CKMB per patient by the various geographic regions. Now, in GUSTO the only comparison we have is

North America and Western Europe. These are the medians with the interquartile range in parentheses. You can see that the median CKMB in North America was four, the interquartile range given here, compared to three in GUSTO II, Western Europe five, three, Latin America four and five. So, we think we actually did a pretty good job of getting enzymes in this trial that were then available to the Clinical Events Committee for review.

DOCTOR DiMARCO: Again, going back to the protocol, the protocol really described a Clinical Events Committee that was independent and blinded, and by your presentation it turns out that it is mostly two cardiac fellows, is that correct?

DOCTOR HARRINGTON: The Clinical Events Committee, the review --

DOCTOR DiMARCO: I'm told two Duke cardiac fellows, so --

DOCTOR HARRINGTON: -- actually, the fellows came from all over the country. We used fellows from a variety of Steering Committee sites, including Cleveland Clinic, Baylor, Mayo Clinic, et cetera.

But, yes, the primary review, as we've used in all of our trials, has predominantly been done at

the Phase I level by cardiology fellows who have completed their clinical training and who are in their research part of their training. So, these are fully clinically trained cardiology fellows.

As part of that understanding that these are, in fact, fellows, we instituted the quality insurance review by the Faculty Committee. Of the ten percent of cases that go to the Faculty Committee, a couple of cases are overturned by the committee, but virtually none have been overturned, and this is very much in keeping with GUSTO II, the IMPACT trials, previous trials with other platelet agents, et cetera.

So, the system has evolved over about the past seven or eight years to where I've described today.

CHAIRPERSON PARKER: Just so I understand, it wasn't always the same two cardiology fellows.

DOCTOR HARRINGTON: That's correct.

CHAIRPERSON PARKER: How many people were involved in the adjudication process?

DOCTOR HARRINGTON: There was approximately ten cardiology fellows that were involved in the process. We tried to use the same group per trial. They undergo detailed in-servicing by the faculty director, as well as the principal investigator of

that particular trial, and there's a lot of checks in place whereby they can ask questions as to specifics of the protocol, et cetera.

We used the same Faculty Committee for the entire trial as the second level review.

DOCTOR DiMARCO: Another question is, when you did, or at least you did a safety analysis after about 4,000 patients, but it also says that you also looked at the data at that time, at some point, even though it was not included. And, when I look at the event rates that are given on page 131 and then given on page 61, the event rates for the first 4,000 patients look considerably less, now maybe someone can tell me the statistical significance, than in the complete trial, and I find that surprising, because it looks like you must have had maybe a 25 percent higher event rate in the second, in the second two thirds of the study, or the latter two thirds of the study, why did that occur, particularly, since at the beginning you had no difference between groups and then later with a higher event rate in the second part of the study you do see a difference.

DOCTOR HARRINGTON: Two issues, the first of which is what took place at the interim review. At the interim review, that was specified to determine

the dose, it was just safety issues that were looked at. Bleeding was available, and I'll point out that although it took place at 3,200 patients, 3,200 patients worth of data was not available yet because of the -- you know, the logistics of getting the data into the coordinating centers, but a substantial amount of data, close to 3,000 patients, was available for review.

Safety was looked at, bleeding, as reported by the investigator, strokes, as reported by the investigator but not yet adjudicated by the committee, so suspected strokes, and mortality. At the time that the committee made the decision they did not have access to myocardial infarction to make that decision, and they did not have access to the composite of death and myocardial infarction, so it was mainly based on safety.

The deaths that had occurred by that point of their review were, I think, approximately 13 in the placebo group and 15 in each of the two eptifibatide groups.

We also point out that the event rate was lower at that point than we subsequently saw, it was approximately 13 percent versus about 15 percent that we saw later on.

DOCTOR DiMARCO: Well, later on you must have seen 17 percent.

DOCTOR HARRINGTON: Because when you -- right -- if you look at when different sites came up, predominantly early on, this was U.S. representation, so some of what we are seeing are some of the geographic variations in the event rates. The United States came up first, and a large portion of that 3,200 patients represents the United States' experience and the early Western Europe experience. As the trial went on, then there were, you know, more sites coming up successively over that 13, 14-month period of enrollment.

DOCTOR DiMARCO: I'm sorry, was there a difference in sites geographically, in terms of event rates? I didn't see that.

DOCTOR HARRINGTON: In terms of the -- we can show you the treatment effect by the geographic region.

DOCTOR DiMARCO: What were the placebo, were the placebo rates different from various areas?

DOCTOR HARRINGTON: They varied across the geographic regions. We can pull that up for you, if you'd like to see it. Do you want to see that?

DOCTOR DiMARCO: Yes.

DOCTOR LINDENFELD: Yes.

DOCTOR HARRINGTON: Could we have slide 65? You can see, this is the death and myocardial infarction at 30 days by geographic region. These are the Clinical Events Committee adjudicated results, and what you can see, the absolute event rates here, event rates in Eastern Europe of almost 20 percent in both groups, 21 percent eptifibatide over the United States, mainly representing North America, 4,000 of the 4,300 patients, 15 percent. So, some variation, 14 percent, 15 percent, almost 20 percent.

DOCTOR DiMARCO: So, what you are saying is the higher rate is mostly coming from Eastern Europe.

DOCTOR HARRINGTON: There is a higher event rate in Eastern Europe, that's correct.

I think Kerry Lee might want to have a comment here.

DOCTOR LEE: John, if I could just comment with regard to the question you've raised concerning the appearance of lower event rates in those earlier patients. There are two things I would emphasize. One is, you'll recall that in the early phase of the trial we did not enroll patients over the age of 75. There was a cap on that until we had some experience with the safety profiles of these drugs.

So, the population of patients in that first -- that early part of the cohort did not include elderly patients, that's point number one.

Point number two is that, at the time that the Data and Safety Monitoring Board reviewed the data to make the decision or the recommendation about going forward with one of the dose arms, we had very little adjudicated information, and as you have seen and will see, perhaps, further, the event rates are higher when we include the adjudicated data than they are based on the investigator assessment alone, and it was that investigator assessment alone data that provided the predominance of the information that was available at that key meeting of the Data and Safety Monitoring Board.

DOCTOR KONSTAM: Could I follow up on the geographic issue?

DOCTOR HARRINGTON: Yes.

DOCTOR KONSTAM: I know you are going to get into the issue of the patients undergoing intervention later on, but just while you have the geographic spread up there, can you tell us how much of that difference by geography was driven by difference in intervention occurring or explainable on the basis, because I'm sure there was an enormous

difference in the interventional rates across the geography as well.

DOCTOR HARRINGTON: Yes, it's a good question, Doctor Konstam.

If you look at the point estimates here, in fact, the point estimate favors placebo for both Eastern Europe and Latin America, and as I point out there's broad confidence intervals. When you do a formal statistical test, looking for heterogeneity amongst the regions, in fact, that test is not significant.

So, there's a possibility that the treatment, as a matter of fact, could go the other way. There are other issues that we've looked at. Part of that I think you'll get at in the next speaker, when we do go through, there are some pretty broad differences in the interventionally treated groups by the region.

I'll also point out that there are some baseline demographic differences amongst the regions, that patients are a little bit different. In Eastern Europe, almost 50 percent of the patients are female. In Eastern Europe, there is almost double the reported rate of heart failure at the time of enrollment, 20 percent versus ten. There's a difference in the use

of Heparin. In the United States, 98 percent of the patients get treated with Heparin, in the other regions it's in the low 80s to below 80, so there are some differences, both in the treatment decisions, as well as in the type of baseline characteristics these patients had.

DOCTOR KONSTAM: Okay. Well, maybe we'll get back to it when we are talking about the interventions, but I really am interested in this question of the differences in intervention rates by geography, and granted not statistically significant difference in the ratios across geography, but it looks different to me, and I just wondered how much of that is driven by the interventional differences.

DOCTOR HARRINGTON: Right.

DOCTOR KONSTAM: And, we can deal with it later or now, but I'd like to focus back in on that.

DOCTOR HARRINGTON: I think it will help you a lot to see the next presentation for that question.

I agree with you, I mean, the investigators look at this as well, and look for what those differences might be, and the differences in intervention, in particular, are striking.

DOCTOR LINDENFELD: Just along that same

line, can you tell us, since there was this gender difference, how many women compared to men had an intervention?

DOCTOR HARRINGTON: Again, it's region specific, and if we look at the gender --

DOCTOR LINDENFELD: But, just across the total study.

DOCTOR HARRINGTON: -- it's roughly the same, about 25 percent of the overall population had intervention and women are roughly the same.

CHAIRPERSON PARKER: Lem?

DOCTOR MOYÉ: Just to avoid confusion, the analysis that we have seen, and all the analyses that we have seen have been intention to treat?

DOCTOR HARRINGTON: This is the all randomized patient analysis.

DOCTOR MOYÉ: Every patient that was randomized --

DOCTOR HARRINGTON: Is included in the analysis.

DOCTOR MOYÉ: Okay.

Well, I apologize if I missed this, but I didn't see any report, I don't remember seeing a report, about vital status, or infarct status at trial's end, did you have any patients with unknown

vital status here?

DOCTOR HARRINGTON: We can show you that.

DOCTOR MOYÉ: Okay. If I missed it, I apologize.

DOCTOR HARRINGTON: It's a very small number of patients, I think in the 30-day period it was about 22 randomly distributed that were not -- of the 11,000 that we did not have the -- 20 patients, do you have that slide? I think it's slide 20.

Here you see on the top line is the patients randomized, lost to follow up at the 30-day period, 22 patients, with a distribution amongst the groups, and then the other ways of looking at the data, how many patients were not actually treated, as Doctor Tcheng already alluded to, 99 patients out of the total sample.

DOCTOR MOYÉ: Well, you are certainly right, that's a small proportion of the number of patients randomized, but maybe a more realistic examination is to compare that number with the number of events you had in the groups, because it may be they are making assumptions -- no, let me just ask to make sure I'm not making the wrong assumption, lost to follow up means you don't know whether they were alive or dead at 30 days, is that right?

DOCTOR HARRINGTON: That's correct.

DOCTOR MOYÉ: So that, therefore, we could make assumptions, differential assumptions about the patterns of death that might be, we don't know, but that might be, that would change our interpretation of the results of the trial.

DOCTOR HARRINGTON: That's correct.

DOCTOR MOYÉ: We could assume, for example, that all the patients, the 14 patients -- well, actually, the high dose mass here, the 12 patients in the Integrilin high dose if they, in fact, died, what impact would that have on your p value?

DOCTOR HARRINGTON: I'm going to defer to Kerry Lee here, who is at the microphone.

DOCTOR LEE: Thank you.

This is an important issue, and I appreciate the fact that you've raised it, and I'd like to just add a little more perspective, if I could, please.

You see in the high dose eptifibatide arm there were 12 patients, eight in the placebo, that's a total of 20 patients in these two primary treatment arms with missing 30-day status.

Now, with the exception of one patient, one of the 12 in the eptifibatide arm, all of these 20

patients were followed through hospital discharge. It wasn't as if they were immediately lost, we had data through hospital discharge, the period of time when most of the events are occurring in these patients.

And, with regard to several of the other patients, we actually had data beyond 20 days. So, we just didn't get the 30-day contact in several of these patients. So, that's one point. We did have some follow-up data through hospital discharge and no events occurred in these patients.

Secondly, in the process of the collection of the longer term follow-up, subsequent to the closure of our database for the 30-day data, but in the process of collecting additional six-month data, we have now obtained additional information even on some of these patients that were lost. For example, there are four of the 12 that are known to be alive and event free, three of the eight in the placebo arm we now have follow up, known to be alive and event free. So, this 22 patients, when you really evaluate the information that we have at our disposal, reduces to a very small number, which I think is a remarkable accomplishment in a trial of nearly 11,000 patients.

DOCTOR DiMARCO: If you did a worse case, though, and all the placebo patients are alive, and

all the Integrilin patients are dead, what happens to your p value? Is that --

DOCTOR LEE: I think that that's a very, very severe, and stringent, and unlikely scenario. If you do that analysis it's likely the p value will lose its significance. But, I think the likelihood of that scenario is so small and so remote as to not merit extensive consideration. I think there are intermediate sensitivity analyses that one could do, for example, to take the placebo event rate, apply that to the Integrilin arm and look at that.

DOCTOR DiMARCO: But, the fact that they are lost tells you that there is something funny about them, so --

DOCTOR LEE: Well, in a trial of 11,000 patients, John, the fact that we've been able to obtain this information on all but .1 percent of these patients, as I say, I think for a study involving the international collaboration that was involved in this trial is remarkable.

DOCTOR MOYÉ: Well, I don't think anybody wants to take away from the gigantic effort that you have undertaken to randomize patients in so many different countries is certainly a worldwide effort.

But, we can't fall into the trap of

thinking that there is some protection in large numbers, that is to say that we can lose a patient here or there because we've randomized so many, because in the end what it comes down to is not the number of patients who are randomized for this issue as are the number of patients who had events. And, the number of patients who had events is a very small proportion of the 11,000 as well.

And, as we can see in a trial where the p value is essentially at the margin, then any assumption that we make about that would increase the number of events in the treatment group can push us over the edge. In fact, I mean, I think that one conclusion is, is that in the clinical trials you have to treat every patient like that patient is the patient that makes the difference, because if you don't you are going to wind up in a situation just like this, where an assumption about a small number of patients, eight patients, because you do know about four of the 12, you do know that four of them are alive.

DOCTOR LEE: We do, yes.

DOCTOR MOYÉ: So, it comes down to a decision about eight patients out of 11,000 patients, assumptions about those eight patients can make the

difference in whether this trial is considered a success or not.

DOCTOR LEE: If you were to assume that all patients, all of those eight patients died --

DOCTOR MOYÉ: Admittedly harsh assumption.

DOCTOR LEE: -- and that none of the patients where we are missing data in the placebo arm had an event, admittedly, a very extreme case, then this may alter one's interpretation of the degree of significance.

DOCTOR MOYÉ: Right.

DOCTOR LEE: If you took a more realistic scenario, however, and said, let's take the placebo event rate and apply that to the Integrilin arm, and assume that that many events occurred in the Integrilin arm, that no further events occurred in the placebo arm, the p value is still .049, and I think that's quite a realistic scenario to assess the sensitivity of these results.

DOCTOR MOYÉ: If we made even the assumption that one or two of the active group patients died, that would be -- that assumption, somewhat milder than assuming all eight died, even that would increase the p value above the margin?

DOCTOR HARRINGTON: That's correct.

CHAIRPERSON PARKER: Can we have a little bit of exploration as to what that margin is, because the committee is being asked a number of questions, eight of them, as to what rules guided the interim analyses, and this is probably as good a time as any to explore those issues.

So, Lem, do you want to -- do you have any questions about that, because we are -- the Agency is asking us specific responses to specific questions very early in the process, when we get to the questions, and I want to make sure that the issues here have been explored for the entire committee.

DOCTOR MOYÉ: Okay.

I think maybe the best way for us to proceed, because this is a fairly complicated topic, is if the sponsor could choose someone to describe to us in great detail, with some clarity, exactly what occurred during the interim analyses, how many there were, what decisions were made, and on what basis was the decision made -- excuse me, what strength of evidence was required from the data to come to the conclusion that one of the arms should be discontinued, with particular attention to, I think, Amendment 6.

DOCTOR HARRINGTON: Kerry, I think, is

going to take care of that.

DOCTOR LEE: I'll be happy to address those questions.

Let me preface my comment, however.

CHAIRPERSON PARKER: Kerry, if you could speak into the microphone a little bit, I think, apparently, there's some difficulty hearing you in the back.

DOCTOR LEE: All right, I'll try to speak up.

With regard to the point that was previously made, I believe that if -- with regard to the assumptions on the patients that were lost, just before we leave that issue, if two of those eight patients died in the eptifibatide arm, and none of the placebo patients had an event that would increase the p value to .049.

CHAIRPERSON PARKER: But, before we -- it's .049 compared to what p value?

DOCTOR LEE: .05.

CHAIRPERSON PARKER: I don't think so.

DOCTOR MOYÉ: No, there's an adjustment that has to be made for interim looks, which suggests the p value is .07?

CHAIRPERSON PARKER: .0478 is the

threshold.

DOCTOR LEE: Well, again, this is an interesting question that we could have some debate about, particularly, with the statistical -- the FDA statistical reviewer, who may wish to offer some commentary on this. We've not been able to duplicate, I must say, the results in the statistical review that resulted in the statement that one would need a p value of .047 in order to declare significance at the end.

The boundaries that were designed, the sequential monitoring boundaries that were designed for this particular trial, were done in such a way that there could not only be early termination of the study for a positive result, but also early termination for rejecting the null hypothesis or the alternative hypothesis. And, these are asymmetric boundaries, and they were very carefully calculated, so in the end one could do this final comparison at exactly the .05 level.

DOCTOR MOYÉ: That suggests to me, though, that there is no penalty for early looks.

DOCTOR LEE: There is a penalty for early look.

DOCTOR MOYÉ: Even though the final alpha

is the same as though there were no looks.

DOCTOR LEE: But, it's accommodated for and taken into account by the overall structure of both of these boundaries, the upper boundary and the lower, which had the lower boundary been crossed early, and thereby rejecting the alternative hypothesis that we had a treatment effect, this has some impact on the overall level of significance. And, rather than get into a lengthy debate about this, this was very carefully calculated and worked out and specified, clearly specified, in the study protocol in considerable detail, as to exactly what these boundaries would be and how they were derived.

DOCTOR MOYÉ: Now, when these boundaries are derived, though, you build in the opportunity to make a decision based on the strength of the data, and at the prespecified times you choose to evaluate the data in order to make a decision.

Now, are you saying then that the alpha that you spent when you examined the data at each of these prespecified times does not have a measurable impact on the alpha remaining for the final analysis?

DOCTOR LEE: There's no penalty at the end because, again, of the way that this lower boundary is constructed, both the upper and the lower boundaries

constructed, that allow us or provide guidance for terminating the study early and rejecting the alternative hypothesis.

DOCTOR MOYÉ: But, still, you make decisions at, what is it, one sixth of the time, I think, and two fifths, and three fifths, you still make decisions at those points.

DOCTOR LEE: Right.

DOCTOR MOYÉ: I guess I'm not sure where the alpha is going. I mean, I appreciate careful derivations, but I just don't know -- if you have .05 to spend overall, and you are looking early, appropriately, and, again, prespecified, then it seems to me that the .05 alpha that you had totally allocated some of that has been used up.

And, by most rules that I've seen that there, therefore, has to be a correction at the end so that the analysis in the end isn't at an .05 level, but at a somewhat smaller level, sometimes not much smaller, but at a smaller level.

DOCTOR KONSTAM: Can I just, Lem --

DOCTOR MOYÉ: Yes.

DOCTOR KONSTAM: -- I'm not sure what we are debating about. The overall nominal p value was what, .042, so this issue only comes up --

DOCTOR LEE: That's right.

DOCTOR KONSTAM: -- with this correction that we're trying to impute for the loss of vital status, which might move it over, but how important is that? I mean, the overall nominal p value is .042, which satisfies both issues.

DOCTOR MOYÉ: Right.

DOCTOR KONSTAM: It satisfies even some penalty.

DOCTOR MOYÉ: But, even with the .042 --

DOCTOR KONSTAM: Right.

DOCTOR MOYÉ: -- you are making -- or people make assumptions about unknown vital status.

DOCTOR KONSTAM: I understand that.

DOCTOR MOYÉ: So, I'm just saying that alternative assumptions about unknown vital status lead to alternative p values, and, therefore, different conclusions about the efficacy demonstrated in the trial.

DOCTOR LEE: I think that's a good point to move forward, you know, the study met the significance criteria, regardless of whether it's .047 or .05. Maybe the thing I could do to move this forward is to describe to you what happened at the interim analyses.

CHAIRPERSON PARKER: Hold for one moment.

Doctor Ganley?

DOCTOR GANLEY: Yes. I guess the only concern I have about that is, what they are essentially saying, that if this drug is actually worse than placebo we are going to stop the trial. Okay. So, we somehow preserve or gain some alpha back by doing that, and that's, essentially, what they are saying, because they are creating this boundary for an alternative hypothesis, so we're somehow gaining back some alpha because we may stop the trial.

DOCTOR KONSTAM: But, based on --

DOCTOR GANLEY: Now, every trial that I've ever reviewed that had mortality, they are always looking at that. Some of them will have some criteria, but I've never seen anyone gain back alpha and protect alpha by that methodology.

DOCTOR KONSTAM: Can I just ask, so then what p value would you like to see satisfied in order to penalize the observations for the early looks?

DOCTOR GANLEY: Well, I think I have to go with what the FDA statistician --

DOCTOR KONSTAM: Which was .047?

DOCTOR GANLEY: .0478.

DOCTOR KONSTAM: Okay, which is satisfied by the nominal p value of the overall trial before you

start making the corrections for the loss of vital status.

DOCTOR MOYÉ: Right.

DOCTOR KONSTAM: Just to clarify.

DOCTOR MOYÉ: Every p value has some assumption about vital status.

DOCTOR KONSTAM: Right, I understand.

CHAIRPERSON PARKER: Okay.

DOCTOR MOYÉ: I guess we got into that, though, just to begin to hear about the decision process.

CHAIRPERSON PARKER: Yes. This is one of several issues that the Agency is asking the committee for guidance about, and one of them was what the degree of preservation of the type 1 error rate was, so we've dealt with one component of that, and I guess, Kerry, you can continue.

John, did you want to make a comment on the previous issue on the critical p value, because we are just about to go into other issues related to the preservation of type 1 error.

And, the only reason we are spending so much time on this is because the questions from the Agency are, in large part, directed to these issues, so in order for us to be able to respond to the

Agency's questions we need to get clarification on as many of these responses as possible.

Lem, go.

DOCTOR MOYÉ: I had just asked that we would hear the interim analysis.

DOCTOR LEE: Sure, these are excellent questions, because this is somewhat of a novel design, dropping an arm, and the way it was done in this particular trial.

In terms of the interim analyses, let me describe what happened, and group them, first, into the interim analyses that were performed where data were evaluated for safety review. There was concern with the high dose that was being administered in the high dose arm of this trial about potential safety problems. The study was started with patients only under the age of 75 years being enrolled. The DSMB was charged then with looking at the safety profiles of the different arms at an early stage to make a judgment as to whether to raise this age ceiling and allow patients of any age thereafter to be enrolled.

The first set of data was presented to the committee after we had safety information on about 300 patients, and already, at that early point, there was a sufficient amount of bleeding that the Data and

Safety Monitoring Board said we'd prefer to see a little more data, safety data, bleeding data, before we make a recommendation that the upper age limit be lifted.

And so, a month later we provided them with some additional safety data, information on a little over 500 patients, and there remained some residual concerns, particularly, about bleeding in lighter weight patients. So, they said let's continue to accumulate some experience, look at the data again.

So, a month or so later, after we had safety information on about 900 patients, the committee reviewed that data, they requested at that particular time some additional analyses, which were performed and a week later a subsequent follow-up call occurred, and at that point then the committee made a recommendation that the upper age limit could be lifted, but they also expressed concern to the investigators about bleeding, particularly, in lighter weight patients.

So, there were four occasions when there was discussion with the committee about safety in this early part of the trial. On the last two of those occasions, they didn't see any new data, they just simply saw additional analyses of data, of previously

presented information. So, there were four of those occasions.

Then, the next major interim evaluation occurred for the purpose of making this recommendation about dropping one of the arms. That occurred when just over 3,200 patients had been enrolled, but we had safety data on about 2,400 patients, and that was the basis for this particular review.

The Safety Committee was presented extensive bleeding and stroke data, and in addition they were also given information about mortality, as part of their safety evaluation.

They did not see any data on myocardial infarction, and based on the safety information that they had they felt comfortable in reaching the decision that had been outlined in the study protocol, that unless there was a safety problem the strategy was to go forward with the high dose arm. That was the preferred course of action, and that's exactly what transpired.

There was one additional efficacy analysis when we had efficacy data on approximately 50 percent of the patients enrolled in these two doses that went forward through the end of the trial.

DOCTOR MOYÉ: I guess I just need to ask

you what will probably be an easy question for you, and, that is, there was a statement, I think, in an amendment that allowed the DSMB to continue both active arms, even though they may have decided that, in fact, patients would not be harmed by the higher dose, they decided to continue both arms, is that correct or not?

DOCTOR LEE: That is correct.

Before we came to the point in time where that meeting occurred and they reviewed the safety data to decide whether to go forward with the high dose arm, there was some concern in the earlier meetings that had been expressed by the committee as to whether they would be able to make this recommendation solely on the basis of safety data.

There may well have been a need to assess the risk benefit trade off and actually see efficacy data and make this somewhat more complex decision. And so, the Steering Committee felt that if they were unable to make this decision on the basis of the safety data alone, that it would be preferable to go forward with all three arms.

DOCTOR MOYÉ: Which did not happen.

DOCTOR LEE: Which did not happen.

DOCTOR MOYÉ: Right, right.

And, even if they had gone forward with all three arms, they made the statement that the final analysis would only be placebo versus high dose, is that correct?

DOCTOR LEE: That is correct.

DOCTOR MOYÉ: Okay.

So, in essence, what we have is in the initial protocol the investigators agreed to do one comparison between the dose that was continued and placebo, and in the end that's essentially what they did.

DOCTOR LEE: That's exactly what they did. The protocol and the intent of the protocol was followed precisely, as outlined.

DOCTOR MOYÉ: Okay, and there were some amendments and conversation in the interim, but that's what they did.

Is it also your point then that you think it's appropriate not to be penalized for type 1 error, even though decisions were made in the interim in this trial?

DOCTOR LEE: I do feel that it's not appropriate to take a penalty for the type 1 error for this particular decision of dropping the low dose.

The justification for that is that, first

of all, they did not make this decision on the basis of the efficacy data.

Now, it is true that they had mortality information available to them, and mortality is one of the two components of the primary endpoint, and so you might say, well, as a result of their seeing that data there ought to be some sort of penalty involved, because if they had seen, potentially, a large disparity in the mortality rates between the low dose arm and the high dose arm, this might have triggered a different course of action.

But, we know that mortality is not the driving factor in this primary endpoint, in terms of discerning differences between Integrilin and control. The difference, really, in the efficacy of this drug is being driven by the myocardial infarction.

So, the likelihood or the probability that the committee would have seen something in the mortality data that triggered a different course of action, I think is so remote that there's no adjustment required for that possibility.

CHAIRPERSON PARKER: But, Kerry, it could have actually turned out differently. It could have been that MI would have been neutral, and all the action would have been in mortality and, therefore,

the provision of mortality data had the potential of exerting an influential effect, and even neutrality of mortality data has an impact on decision-making if one is trying to assess risk to benefit.

And, just to clarify that, mortality data was not available to the committee for any of the three/four sort of safety analyses that occurred for 900 patients.

DOCTOR LEE: No, it was.

CHAIRPERSON PARKER: It was.

DOCTOR LEE: The mortality data was provided for those safety reviews as well.

There were not many deaths, I must say, it was a very small number of events, and the focus of those reviews was really on the bleeding data.

CHAIRPERSON PARKER: But, they did receive the mortality information.

Can we just have one clarification? The FDA calculation of the alpha left for the final analysis of .0478 is based on how many interim analyses?

DOCTOR GANLEY: I don't think Doctor Nuri is here. Oh, there he is.

DOCTOR NURI: This is Walid Nuri.

Actually, in reality, there were only two

interim analyses, and the calculation was based on that, and the final analysis came out that after applying the Barr and Fleming formula for calculating the alpha spending came out the final alpha should be .0478.

DOCTOR MOYÉ: .0478 was the remaining alpha in your estimation?

DOCTOR NURI: Remaining alpha.

CHAIRPERSON PARKER: That was based on what would be left for two interim analyses plus a final analysis.

DOCTOR NURI: That's right, yes.

DOCTOR LEE: I might just say that our calculations were based on the three interim analyses that were outlined in the study protocol.

I might also invite, if you wish, Doctor Lloyd Fischer to come forward and comment as a member of the Data and Safety Monitoring Board, who was involved in the review of the data, as this unfolded.

DOCTOR FISCHER: Yes. With regard to the choice of the dose, I have a very clear memory because, actually, I argued very vehemently that we should be allowed to look at efficacy as well as safety data, because to me it was like the sound of one hand clapping and what you really want to know is

clinical benefit.

And, I went to -- I was quite obnoxious about it, and those of you who know me can readily believe that, but I went to the point of even forcing an extra phone call to try to talk them into it, and they would not do it. They were adamant that they didn't want to pay any penalty for power, and the reason they were doing this was, as you heard, there wasn't sufficient safety data at the high dose, but this was not really an interim look.

Kerry was very good about not supplying us with any of the data, and they stated during this phone call that even if there was a trend one way or the other on mortality that should not be a cause for not -- basically, based upon the PK data and the amount of inhibition of aggregation, they wanted us to use the high dose, and it was perfectly clear that was everybody's intent, and it was only if there was some horrible safety problem that that should not be done.

And, I imagine, I don't know the history of this, but I imagine part of the reason this might have been institute is to try to convince the FDA that there was adequate regard for patient safety when they really didn't have a huge amount of data to base the choice of this dose on.

So, I just wanted to reinforce.

Furthermore, although I, at least, thought about the fact that we did see mortality and it could relate to efficacy, my guess is, many of the clinicians on the committee didn't think of it that way. I don't want to disparage clinicians, but statisticians tend to think about all the ways to do -- you know, how anything relates to anything, but it really was a safety concern.

And, if I could just take the opportunity to introduce two other points. One is the loss to follow up. Both Lem and I have been involved in large studies, BHAB, the Cass study and so on, they did better than we did, on the other hand, they didn't have the same length of follow up. And, it's true when you are near a boundary, conceivably something could happen.

Within the Cass study, the people who were lost to follow up, eventually we located some of them, and the reason we lost them there was because, not because of bad things, but because actually they were much more mobile. So, I would suggest the most likely scenario is, we used 11,000 people, some of the people got out, were discharged after the event, and they felt relatively healthy, but they were aware of their

own mortality and they said, gee, I'm going to go visit my children somewhere, I'm going to go do whatever, and people tried to contact them and they just weren't around. That, to me, is the most likely scenario.

And, finally, a third point, since these meetings are didactic, for industry, I want you to perform a slight thought experiment. Suppose you had a randomized trial and one of the clinics was in Seattle, and Mount Ranier blew, and it's still an active volcano and the last time it blew there was 14 inches of ash on Seattle, so we sort of had a Pompeii there.

Fortunately, there was enough data at the other clinic, so the sponsor came in to the Agency and they said, well, we don't have the Seattle data, Mount Ranier blew up, but we see no reason to think that response ought to relate to the eruption of Mount Ranier, we'll present these data, and we would all agree this was a reasonable thing to do and there's no introduction of bias.

Or, if you don't like Mount Ranier, if you are a Californian, the big one hits and your city falls into the sea, unless you think you are safe here on the East Coast a meteor hits and takes out New York

City, whatever. The point is, you can remove patients from an intent to treat analysis if the removal clearly has nothing to do with treatment assignment. You do not introduce bias, that's the point Tom Fleming was making earlier.

So, if you -- I was involved in another setting with a drug, where they were to give oral medication, and it was a transplant setting, and because of the setting many people could not take their medication because they just could not swallow oral medication.

To me, that is independent and the lesson to be learned from this, for people designing future trials, is you do not randomize at the time of informed consent, you don't even have to randomize when you start to prepare a drug, if it has to be infused and you have to have it there in case a patient can take it, provided you have adequate safeguards so people can look at the formulation and somehow detect what's done randomization should begin just at the moment they take it, actually, and if that had been done here I would suggest, this is back to the IMPACT trial, that there wouldn't be an issue.

But, the moral of the story in my mind is to avoid future conflicts like this, if we do our

studies in what to me is the most -- the best way to align the intent to treat biologies, you know, so that they are going the same ways, you always want to analyze at the very last possible moment.

DOCTOR KONSTAM: Can I just, Lloyd, while you are still up, it seems that there are two points about that. You know, one is, is the analysis valid, and you'Ve made that point. The other is, what analysis do you plan to do.

DOCTOR FISCHER: Absolutely.

If you are looking at both and take the best one --

DOCTOR KONSTAM: Yes, right.

DOCTOR FISCHER: -- which a sponsor will tend to do.

DOCTOR KONSTAM: Well, I'm a little concerned about that, because we've heard there was a letter sent to the FDA stating that that was the way that the intention was.

I noticed that that wasn't the way the primary analysis was done in this last trial that we saw, so that's sort of another aspect of this. I'm concerned that this -- whether this really was the principal analysis that was planned.

CHAIRPERSON PARKER: If we could, because

we are now drifting to PURSUIT, and I think that for better or for worse I think that we all think that the all randomized analysis, and I think, Lloyd, you would agree with this, that it's always a good thing to randomize as close to the intervention as possible, in order to minimize the questions that would be raised as to whether the removal of patients is informative or not.

DOCTOR FISCHER: Absolutely, because if you can introduce bias those patients can only add noise to the comparison.

CHAIRPERSON PARKER: Okay.

So, whether or not one -- it's difficult to know how much more confidence we can gain on this issue.

DOCTOR KONSTAM: Well, just with regard to the PURSUIT study, however, there was adherence to the true intention to treat by randomization analysis, is that correct?

DOCTOR HARRINGTON: Right.

DOCTOR KONSTAM: I mean, just to contrast the two, that's the question I'm raising.

DOCTOR FISCHER: To be absolutely honest, I don't remember the details of that, and somebody who does should give you a correct answer.

DOCTOR KONSTAM: I'm just curious why there was a different primary mechanism of analysis done in the two trials.

DOCTOR KITT: Just to be real clear, the rules were the same for both IMPACT II and for PURSUIT, in fact, the report that we sent FDA was the identical analysis that you saw for IMPACT II. FDA recommended, however, that for this committee that we provide, particularly since there truly is no difference, and we can show you all the data for both analyses if you'd like, but we specified exactly the same criteria, both the treated as randomized population and the technical intention to treat analysis in the PURSUIT study. So, we did not change between studies.

CHAIRPERSON PARKER: But, what -- in the -- I think that the protocol in both trials clarifies that the all randomized patient analysis is what you would be held to, the only difference between the two, correct me if I'm wrong, is that for the PURSUIT study, after the trial was completed, but before the trial was broken, a letter was sent --

DOCTOR KITT: IMPACT II.

CHAIRPERSON PARKER: -- IMPACT II, did I say PURSUIT, I'm sorry, is that correct?

DOCTOR KITT: That is -- I have to think what you said, that is close to correct, yes.

CHAIRPERSON PARKER: Okay.

Doctor Ganley?

DOCTOR GANLEY: Yes. In the PURSUIT protocol, which is on page 45 of the book that you had, it says the comparison will be performed for two patient populations, all patients who are randomized and all patients who are randomized and subsequently receive treatment. So, we automatically take the worst case scenario there and take all randomized.

CHAIRPERSON PARKER: Right.

DOCTOR GANLEY: It doesn't specify one over the other, it just --

CHAIRPERSON PARKER: I understand.

Let me see if we've gone through the issues.

Lem?

DOCTOR MOYÉ: Yes, just one final question. I wonder, Kerry, if you could distinguish the procedure that was followed for discontinuing the low dose arm from the play the winner scenario, which is, you begin randomizing the three groups, make a decision in the interim analysis which one is better, discontinue the one that doesn't give you the results

you are looking for and then go on to analyze in the end.

DOCTOR LEE: I think the major distinction between what was implemented in the design of this trial and what you've described as the play the winner strategy is the information that would serve as the basis for the decision as to which dose was retained and which dose would be carried forward.

As we've repeatedly emphasized here, the decision in this trial, with the exception of the fact that the committee had access to mortality data, the decision really was driven by safety information, primarily, by bleeding information. That was the driving feature of the deliberations that occurred.

And, it was not on the basis of having available to them efficacy information, in particular, the efficacy information for the primary endpoint of the trial.

And, I think that's a very important distinction.

CHAIRPERSON PARKER: Ray?

DOCTOR LIPICKY: Milton, if you are doing this to be able to answer the questions, an adequate description has now been made. It was missing previously. The reason it was missing was we would

have laid it out but there wasn't enough time to get the reviews done and everything to the Advisory Committee in time, so I apologize for having done this in public.

But, things are laid out, and I don't think you need to lay it out any further.

CHAIRPERSON PARKER: No, I actually think we've explored all of the issues, but, of course, we are not only exploring them for purposes of the evaluation of today's agent, but I think there are questions for the future as to the general policies to be followed for penalties to be taken for interim analyses. What penalties, if any, are to be incurred for a play the winner or drop the loser design, these are all very relevant issues and I understand that there are probably imperfect answers to this, but this is, I think, the first time this committee has had a chance to discuss these issues, or at least some of these issues. And so, it was relevant to do that, not only for purposes of today's discussion, but to provide guidance, if any, for future discussions and analyses.

DOCTOR LIPICKY: It's just that to really provide guidance on each of these issues would require considerable, much more discussion of the issue, and

I think that as I was involved, for example, in the multiple comparisons question, one could devote the whole day to it and still not come up with a definitive answer. So, for the next five minutes, we won't be able to lay out appropriate guidelines, but I think that the details of what was done are now known, and whether or not that influences the inferences you wish to take I think you can make decisions, they may be wrong decisions, but you can make decisions.

CHAIRPERSON PARKER: Okay.

DOCTOR KONSTAM: Can I move on to another question regarding PURSUIT?

CHAIRPERSON PARKER: Yes.

DOCTOR KONSTAM: Can you comment about, I just am noticing these nine patients with severely depressed platelet counts, can you give us some follow up on those patients? Did they rebound and what happened?

DOCTOR HARRINGTON: Two of the patients in the -- the two patients in placebo had major bleeding events, though, did not have hemorrhagic strokes in the placebo group.

In the eptifibatide group, I think one or two of them had a major bleeding event. There were no

CVAs, no MIs and no deaths in any of the patients who had the profound thrombocytopenia. Platelet counts recovered, and there were no -- as far as, you know, the period of measurement out 30 days, there was no adverse consequences from that, so no CVA, no MIs and no deaths in those patients by the end of 30 days.

CHAIRPERSON PARKER: One or two of them had -- two of the patients in the placebo group, not in the active treatment group, a couple of the patients had major adverse events associated with severe thrombocytopenia, can we just talk about that a little bit?

DOCTOR HARRINGTON: Can we have slide 182? Actually, none of the patients in the eptifibatide, none of the nine patients had a major bleeding event, as you can see on this slide, and by chance two of the -- both of the placebo patients, who had platelet counts less than 20,000, did have a major bleeding event.

I also wanted to point out that we have done a fair amount of detective work in these 11 patients, and I'm just going to do a hand count here, two, four, six, seven -- only six of these 11 actually had true thrombocytopenia less than 20,000. There were, when we went back to look at the data, this is

after this was submitted, there were some spurious numbers, for example, one patient had a platelet count that was graded as a one, it turned out to be 1 million, not 1,000. So, there was those types of events.

So, in fact, of those there remained one placebo patient and five eptifibatide patients who had thrombocytopenia. As far as the 30-day outcome in those remaining five patients, none of those patients had either death or MI, one of the primary endpoints.

DOCTOR LINDENFELD: Could you just remind us how frequently platelet count was measured?

DOCTOR HARRINGTON: Platelet counts were measured daily during the infusion of the drug, and then after that at the investigator's discretion.

DOCTOR KONSTAM: Well, okay, but what's your feeling right now, I mean, does Integrilin cause rare, if you want to call it severe, thrombocytopenia or not? What are we going to wind up saying about this?

DOCTOR KITT: It would be my opinion that it does not. I want to bring up some -- I'd like to bring up some supportive information, though, if I could have slide 420, this is from the IMPACT II study. Again, we have another 4,000 patients in this

study, this is the incidence of basically the same analysis that you saw from PURSUIT in the IMPACT II study, albeit with a different dose, and once again you can see that thrombocytopenia, particularly severe thrombocytopenia less than 20,000 platelets, was very unusual in one patient in placebo and one in the 135.5 group, and none in the 135.75.

CHAIRPERSON PARKER: But, this is not a dose you are recommending.

DOCTOR KITT: That's correct. Again, we have to -- you then would have to speculate the mechanism of action.

DOCTOR KONSTAM: Do you want to say something about that? Have you done any investigation to determine what might be the mechanism of action of severe thrombocytopenia with this agent?

DOCTOR KITT: Well, we have done -- we have looked for antibody production with Integrilin, and we've brought this up in a previous briefing book that we had put together for the first committee, and I don't exactly know the number off the top of my head, but in several hundred patients we looked for antibody production, both in the IMPACT II study and in some normal volunteer studies, including retreatment of patients, and we've never been able to detect any

antibody formation to Integrilin.

So, from that mechanism of action, we don't believe that there's any basis for that.

In addition, again, looking at the entire database of over 15,000 patients, if it is there it is at an extremely low frequency.

DOCTOR LINDENFELD: How many patients have been treated with the Integrilin more than once?

DOCTOR KITT: In a deliberate volunteer study, I think it's 21 normal volunteers were retreated.

DOCTOR LINDENFELD: And, the incidence of thrombocytopenia in those?

DOCTOR KITT: There were none.

CHAIRPERSON PARKER: Dan?

DOCTOR RODEN: I have a couple of what I hope will be just very brief questions.

When the protocol was amended, or when the planned amendment was implemented, the elderly were added.

DOCTOR HARRINGTON: That's correct.

DOCTOR RODEN: Were there other changes in the protocol?

DOCTOR HARRINGTON: As you've heard from Doctor Lee, there was a concern of the Data Safety

Monitoring Board that bleeding in the lighter weight patients might be problematic. That was conveyed to the Steering Committee, and around that time our understanding of adequate levels of heparinization was becoming more apparent, and so there was a recommendation made that the light weight patients have dose adjusted Heparin.

So, the very light weight patients, the range of ABTT stayed the same.

DOCTOR RODEN: That was the only other recommendation that was made?

DOCTOR HARRINGTON: That was the only other change to the protocol.

DOCTOR RODEN: Okay.

I want to ask the same question about PURSUIT that I did about IMPACT, and that is, because the statistical significance, as I serve on the NIFAGE and I hesitate to open the statistical can of worms again, there were 99 patients who fell into this funny time period between randomization and initiation of therapy, and who didn't get therapy, did we know what the outcomes in that group are? How many of them had a primary endpoint? Do we have that data?

DOCTOR KITT: I just want to be clear that the analysis you see includes those patients.

DOCTOR RODEN: Okay.

DOCTOR KITT: So, this is all 10,948 patients. In the document provided to FDA, we did divide that out, it's a very small number of patients, and I could find that for you in a second, if you'd like.

DOCTOR HARRINGTON: If you do the as-treated analysis, the significance of the p value actually, you know, is a smaller number.

DOCTOR RODEN: I guess I don't understand why you didn't do the as-treated analysis in PURSUIT, when you went to such lengths, including this famous letter, to implement this as-treated analysis in IMPACT II. A cynic might have things to say about that, I'll just leave it open.

DOCTOR HARRINGTON: I think that a good portion of the answer is a clinical answer, that in the angioplasty state, where we are trying not to interfere with clinical practice, and so we allowed randomization prior to the actual decision that the procedure was going to be done, there were a, you know, sizeable portion of those patients that didn't have a lesion amenable to angioplasty, and they either didn't have that procedure or they had surgery.

In the unstable angina setting, we don't --

it's not an analogous one. These patients were being treated in the emergency room, in the intensive care unit, on the regular cardiology services, and so there wasn't the same issue that treatment was not going to be given because a procedure was not done.

CHAIRPERSON PARKER: It's not quite right, because the patients excluded from IMPACT II included some patients who actually had the procedure. So, it's not quite right.

DOCTOR HARRINGTON: But, the majority of them did not have the procedure.

CHAIRPERSON PARKER: But, it's not quite -- it's not quite exactly what you are saying.

DOCTOR RODEN: I think we can spend all day talking about these 99 patients, and I don't want to do that.

DOCTOR KITT: I can give you the actual number, if you'd like, and this is looking at the total number. In the placebo group it's a difference of two patients, and in the eptifibatide group it's a difference of three patients.

DOCTOR RODEN: Who have a primary endpoint.

DOCTOR KITT: I'm sorry, that was at 96 hour. Two and five, so two in the placebo group, five in the eptifibatide group that would be in that 99, so

percentages of 15.8, 14.3, p value of .034.

DOCTOR RODEN: So, it sounds like again -- well, I won't pursue that -- are you going to have a discussion, are we going to have a discussion, Milton, of the difference between North America and the rest of the world?

CHAIRPERSON PARKER: I think that may be part of the angioplasty discussion?

DOCTOR HARRINGTON: That's correct.

DOCTOR RODEN: So I'll defer that, and we're also going to have a discussion, which I think the answer is pretty clear, but why in IMPACT II the benefit is in the 24 hours and in this study the benefit only starts to become apparent at the two or three, is that just the difference in biologies?

DOCTOR HARRINGTON: I think it's in part the difference of the biology, in part what it is, is in that first 24 hours the clinical difficulty in sorting out the unstable angina population is to whether or not they are having an infarct at enrollment versus an endpoint infarction.

And so, I think it reflects part of the early clinical uncertainty, as well as a big difference of the biology.

DOCTOR RODEN: But, it is sort of --

because one of the questions that we're going to come to is whether these two trials are actually testing the same disease entity, and it is a problem that you see no treatment, or you apparently see no treatment benefit in the first 24 to 48 hours. I'm sure we'll come back to that.

DOCTOR KONSTAM: It's a different endpoint as well in the two trials, and that may be contributing.

DOCTOR HARRINGTON: Different endpoint, and you do actually start to see separation of the curves at the 24-hour period. I think when you get beyond that period of clinical uncertainty, as to whether it was an event at enrollment or post-enrollment event.

DOCTOR LINDENFELD: Maybe you could --

DOCTOR RODEN: One more question, and that is, the issue of -- the six-month data, there's no difference in death rate.

DOCTOR HARRINGTON: That's correct.

DOCTOR RODEN: And, there's a difference, the difference is all driven by MIs.

DOCTOR HARRINGTON: That's correct.

DOCTOR RODEN: MIs are driven mostly by -- and the MIs are diagnosed by some central mechanism up until 30 days, and then a non-central investigator

driven definition after 30 days.

DOCTOR HARRINGTON: That's correct.

DOCTOR RODEN: So, because there is a difference in the way investigators view the world, and the way the Central Committee, so to speak, views the world, if you make some guesstimate of how many infarcts there really were, based on how many infarcts the investigators said there were, there would be more, because that's what happened in the first 30 days.

And, presumably, there will be more in both the treatment group and in the placebo group, and it seems to me that that would, in fact, it's conceivable that because there were actually more events than the investigators thought there were and we're never going to get at that, then the statistical significance of the six-month endpoint might actually be smaller than you think it is.

DOCTOR HARRINGTON: You are correct, what I showed when I displayed the six-month data is the investigator-determined infarction from the time of enrollment until the six-month period for precisely that period, and the p value on that, as I displayed, was .02.

When you do the analysis that you are

suggesting, which I believe used the central adjudication through 30 days, which is what we had, and then the investigator determination after 30 days, the overall relative number of events increases. The absolute difference remains the same, that's still 1.5 or so, 1.3 percent difference, and the p value increases to .09.

DOCTOR RODEN: And so, had there been central mechanisms in place for the entire six months one would have thought a p value of .15.

DOCTOR HARRINGTON: Because the relative difference would have continued to increase, that's correct.

CHAIRPERSON PARKER: We'll go, Ileana, John and JoAnn.

DOCTOR PIÑA: I want to go back to the safety issue with the bleeding, since this product would be used in labs where the practice may be Heparin and Aspirin, and that may take us back to the regional differences. Have you been able to see any interaction between the thrombocytopenia with HIT or Aspirin, in other words, were the bleeding complications more common in those centers that used Aspirin and Heparin versus those centers that did not? I don't know what the practices are in Eastern Europe

or in Latin America, as far as the use of Heparin or Aspirin.

DOCTOR HARRINGTON: With regard to the question of thrombocytopenia --

DOCTOR PIÑA: Or bleeding.

DOCTOR HARRINGTON: -- or bleeding, I'll take thrombocytopenia one first, if you look at the level of thrombocytopenia less than 100,000, less than 50 percent from baseline, the amount of thrombocytopenia is equivalent in the groups.

It would be at least speculated that part of that thrombocytopenia in the placebo group is Heparin driven, as well as other medications, procedural usage, et cetera. We've not sorted out what the contribution by itself of Heparin is to the thrombocytopenia.

With regard to the bleeding question, we do have information on the differences in bleeding around the world that in part reflects the difference in practice around the world, in part represents the impact of Heparin differences around the world. The bleeding rates around the world follow the procedural usage, in other words, the highest bleeding is seen in those regions that employed the most procedures.

I'd also point out that it was in those

regions whereby the greatest treatment effect was also seen, so it's this complex interaction between region, procedural usage, bleeding and efficacy that is still trying to be figured out.

DOCTOR PIÑA: Do you know with those regions where the procedures were the highest, was the use of Heparin and Aspirin also the highest?

DOCTOR HARRINGTON: The use of Heparin was the highest. In North America, and particularly the United States, the use of Heparin was approximately 98 percent. Take the lowest region of the world, where procedures were used, Eastern Europe, and the rate of Heparin usage during study drug infusion was in the high 70s to low 80s range, so a sizeable difference, part reflecting practice differences, part, I think, reflecting procedural differences that have obligatory Heparin usage.

DOCTOR DiMARCO: I'd like to cover a little bit about dosage. We really have, at least as I look at it, we have four clinical data sets where we can compare some doses, and if we look at IMPACT II the slightly lower dose, if anything, looked a little bit better. I'm not saying there's a difference between the two, but certainly there's no improvement with a higher dose than based, I guess, solely on in vitro

data, and you went to a higher dose in PURSUIT, and yet, when we look at the interim analysis, which admittedly wasn't -- which caused you to drop the lower dose, it doesn't seem there's any improvement between -- there's any difference between those two doses. Where does the dose effect start, where do you plateau, how did you select -- you know, are you basing this primarily only on in vitro data? The dose is -- how do we know that half the dose wouldn't work just as well?

DOCTOR HARRINGTON: Michael, do you want to take this?

DOCTOR HOMCY: I think that your point about the 135.5, 135.75, to reiterate what Tom -- Charles Homcy.

DOCTOR DiMARCO: No, I know, just direct the microphone.

DOCTOR HOMCY: Oh, I'm sorry, I'm not as tall as the rest.

The 135 0.5 and the 135 0.75, I think you are absolutely correct, John, that this is really in the middle of the concentration versus platelet aggregation curve in reality. So, we are in the middle of the dose response curve there.

I think that the 182.0 achieves robust

platelet aggregation as defined by the way it is typically defined in these kinds of studies, 20 micromolar ADP, and a high level of receptor occupancy, essentially, wiping out ADP-induced platelet aggregation in the majority of patients at steady state, and gets there very quickly with the bolus.

I think that we also knew at the time, getting back to an insightful question that was asked, getting back to how the dose was picked, yes, we knew about the in vitro data, but we also knew that the pharmacokinetics of this drug were excellently well behaved in terms of dose proportionality, and it was very easy for us to predict based on considerations of that and the age population that we would be treating that we would be approaching the receptor occupancy looked for at the dose of 182.0.

And, if you go back and calculate where you are at 181.3, you are at about 60 to 70 percent receptor occupancy.

So, although we don't have an answer that directly addresses efficacy, we can look at the contemporaneous safety data from the 181.3 dose, because there weren't enough patients when the dose was dropped to look at efficacy, obviously, because

the size of the population wasn't large enough.

But, those are sort of the pharmacokinetics and pharmacodynamic thoughts that went into planning the 182.0 dose, if that's at all helpful to you, and the contemporaneous bleeding of the 181.3 dose is available from the PURSUIT data.

DOCTOR DiMARCO: Yes, just we don't really have any clinical dose response here, is that correct?

DOCTOR HOMCY: Well, we don't compare, in the PURSUIT trial, the middle of the dose response curve that was obtained in the IMPACT II, that's correct.

DOCTOR DiMARCO: The second part of that, Charlie, if we are basing it all on in vitro data, all of these patients are treated with Heparin and Aspirin, as not a platelet scientist, how do you interpret in vitro data which are done in platelets that aren't treated with Heparin and Aspirin, or are they treated with Heparin and Aspirin so that it's clinically comparable for someone?

DOCTOR HOMCY: We've looked at the effects of Heparin, actually, as an anticoagulant, and it's very similar to PPACK. It doesn't really address it, even at higher levels. Obviously, there's the rare patient that has a response to Heparin, but that is

not the case typically, so Heparin doesn't affect the behavior here, although Aspirin has, in various trials, depending on the level of occupancy you achieve, can affect platelet aggregation at the levels we're achieving, Aspirin is not impacting ADP-induced platelet aggregation in any serious way, although at low doses of Integrilin it can affect the bleeding time because of the other mechanisms through which it affects platelets.

DOCTOR HARRINGTON: And, I'll just point out that the PERIGEE data that you saw from Doctor Gretler, those are from patients in the PURSUIT trial whom were treated with Heparin and Aspirin, so the placebo, you know, the control arm versus the active therapy arm, makes that comparison.

DOCTOR LINDENFELD: Just a quick two questions.

Do you know what the mean time to intervention was in this study, was there intervention done?

DOCTOR HARRINGTON: Again, this is another question that varied widely by region, and you'll see that in the next presentation.

In the United States, the vast majority of the procedures that were performed were performed

during the first 72 hours of the hospitalization, whereas, in the other regions of the world the majority of procedures that were performed were performed after study drug termination, and you'll see some broad differences in the next presentation.

DOCTOR LINDENFELD: Because this comes back to the difference of why the timing and the results might have been different in the two studies.

DOCTOR HARRINGTON: That's correct, and you'll see some of that as well in the next presentation.

DOCTOR LINDENFELD: The next question I have is, how many of the -- most of the events were early in this study, within 96 hours, how many of the infarcts were within the first 24 hours? I know half the patients presented with infarction, but how many of those infarcts, repeat infarcts, were within the first 24 hours?

DOCTOR HARRINGTON: If I could go back to my main slide and look at slide 16, we can look at the Kaplan Meier curves, where you can see where the curves --

DOCTOR LINDENFELD: No, just if you can address while you are showing us that how you counseled people to make the diagnosis of a second

infarct in the first 24 hours.

DOCTOR HARRINGTON: -- the definitions that was set up by the Clinical Events Committee took into consideration the uncertainty that exists in the first 18 to 24 hours, and the way that the protocol defined an infarction in the first 18 hours was dependent upon a number of things.

If enzyme levels were negative at zero, eight, 16 hours, and there had been no intervening event, then those patients would not be considered to have had an enrolling infarction, and anything that occurred thereafter would be an index infarction.

If it was the more confusing story, where there were enzymes that were positive in those early time points, the zero positivity, the eight-hour positivity, then you required recurrent chest pain and recurrent ST segment elevation that was documented on electrocardiograms for review.

So, recognizing the difficulty in that early time period, we made the diagnosis of early re-infarction more stringent, and that is that you needed the documented ST segment elevation.

Here I think you -- I'm sorry --

CHAIRPERSON PARKER: Yes, did you want to go through this?

DOCTOR HARRINGTON: -- I mean, I think you can see here that the events are occurring very early, that there is separation of the curves, and if the event rate is 15 percent by about day four here, you've already got two thirds of them, ten percent of the events. So, the events, as you point out, are occurring early, and the maximal treatment benefit is seen early.

CHAIRPERSON PARKER: Was the discrepancy between the investigator and CEC adjudicated events lower or higher if you looked only at the patients with unstable angina or non Q-wave infarct?

DOCTOR HARRINGTON: We've not looked at that. What I can tell you that we've looked at, Doctor Parker, is we've taken the thousand disagreements that existed in the trial, the thousand disagreements are broken up two ways. One way is that the site says there's an infarction, the CEC says no, and the other is the converse, the site says no, the CEC says yes.

And, if you like, I can show you that data as to what the -- we've gone back and looked at this 1,000 patients as to what was the reason for the disagreement, and it, I think, gets at part of your question, which patients were having enrolling

infarcts versus which patients had an event after.

Would you like to look at that?

CHAIRPERSON PARKER: Is it brief?

DOCTOR HARRINGTON: It's very brief.

CHAIRPERSON PARKER: Okay.

DOCTOR HARRINGTON: If we could have back-up slide 477. This is the disagreements, 167, where the site said there was an infarction and, in fact, the CEC, upon review of the data, felt that an endpoint event had not occurred.

I think the point that you were in part making is this confusing group here, the 38 percent of those disagreements upon further review were actually enrolling infarctions, they were people who were having infarctions at the time of enrollment.

If I could have back-up 478. In the group where the site said no but the CEC said yes, the much larger group, you can see what the issues are here. There were a number of events that were being picked up based upon isolated CKMB elevation, without associated ischemic symptoms, that were at least documented for our review, about a quarter of the patients had a documented ischemic event on the case report form, with elevation of the CKMB, and so you see all those added up here.

DOCTOR KONSTAM: Just, hopefully, just one very brief point. You said that some patients got an infusion less than 72 hours if they went home before 72 hours, how many patients approximately, ball park figure?

DOCTOR HARRINGTON: The median infusion was 72 hours. In the U.S., the median infusion was in the high 60s, with a full quarter of the patients getting the infusion in the 36-hour range.

DOCTOR KONSTAM: And, lastly, the adjudication process by cardiology fellows included strokes?

DOCTOR HARRINGTON: The strokes were all reviewed by faculty cardiologists and faculty neurologists.

DOCTOR KONSTAM: Okay.

CHAIRPERSON PARKER: Okay.

Let's proceed to the next presentation.

DOCTOR LINCOFF: Well, it's now good afternoon.

If I could have my first slide, please.

I'm going to focus now on the issue of intervention, and that is the effectiveness of therapy in patients who did and did not undergo coronary revascularization.

If I could have the first slide, carousel four.

Now, the purpose for this analysis is twofold. The first is to establish whether or not eptifibatide was efficacious in both approaches or management strategies for revascularization, that is, was it effective whether or not a patient underwent early percutaneous revascularization.

The second was also to provide a link to the previous IMPACT II study and help provide complementarily of evidence supportive for the indication overall for percutaneous revascularization.

This slide shows the breakdown of revascularization procedures, that is, catheterization, percutaneous revascularization and coronary bypass graft surgery at the three prespecified time points of 96 hours, seven days and 30 days.

Focusing on 96 hours, which is the early time period during which the drug therapy was underway, you can see that 15.7 percent of patients underwent percutaneous intervention overall. Specifically, 1,228 patients in the PURSUIT trial were treated by percutaneous coronary intervention during the study drug therapy. As has been previously noted,

this choice to perform coronary intervention was carried out at the discretion of the operator or the interventionist taking care of the patient was not protocol driven.

Now, aside from the obvious differences between the IMPACT II and the PURSUIT trial with regard to treatment regimens, patients, drug therapies, et cetera, there is commonality, however, with these patients in that the revascularization procedures were carried out during study drug therapy, and, thus, these data are complimentary and confirm the efficacy of eptifibatide during coronary intervention in a broad setting of multiple clinical settings.

This slide again shows a breakdown of the interventional procedures carried out during the initial hospitalization. Overall, 24 percent during the initial hospitalization, most featuring balloon angioplasty as part of the procedure, again, reflecting current clinical practice half of those patients who underwent an intervention received a stent and atherectomy was used rarely.

Now, in any analysis of this type, in which the subgroups are defined by an event which is not randomized, there are significant limitations which

must be acknowledged, and, again, the catheterization and revascularization procedures were not randomized and, thus, the protection of randomization does not extend to the subgroups that are defined by the usage or the absence of usage of early revascularization, due to the risk of multiple confounding factors and of selection bias.

In particular, the selection for the procedure may have been influenced by post-randomization of events. The issue becomes further complicated by which revascularization procedures to include in the analysis. Does one include procedures that include -- that were performed off the study drug, as well as on the study drug, despite the fact that there can't be an expectation of study drug effect. Moreover, how does one include events that occurred prior to coronary intervention?

This is particularly complicated, in that endpoint events may have occurred prior to the coronary intervention, they may have led to the coronary intervention, in other patients they may have precluded a coronary intervention, they may have occurred afterward and been due to a complication of intervention, or they may have occurred despite a successful revascularization.

All of these issues again highlight the fact that this is an observational analysis and statistical inferences can't be drawn.

Now, this somewhat complicated slide outlines the overall distribution of the patients according to randomization to placebo or eptifibatide, as well as their disposition into strategies of revascularization. Now, PCI or revascularization in this and subsequent slides refers only to events occurring with the first 72 hours that is on the study drug therapy, unless noted otherwise in one or two particular slides.

As can be noted, ischemic events could have occurred, and did occur, prior to revascularization, after revascularization or in the absence of revascularization.

When we compare the patients who are randomized to placebo to those randomized to eptifibatide, it is clear that there was a drug effect in each of these settings. Events occurring prior to revascularization occurred in 35 placebo treated patients, and only 11 eptifibatide treated patients, representing a stabilization prior to revascularization with a strategy of revascularization.

Following revascularization, events occurred in 106 placebo treated patients, 73 eptifibatide treated patients, and in the absence of revascularization 639 events occurred in placebo patients, 599 eptifibatide treated patients.

In an effort to try to express the treatment effects in these different settings, I'll present the data in a number of different ways. The two important issues are as follows. If we are considering the strategy that a patient with unstable angina will be treated with revascularization, then all events occurring are worthwhile to consider, because there is a protective effective eptifibatide therapy prior to the intervention being carried out.

If, on the other hand, one is interested only in focusing on the interaction between the intervention itself and the drug therapy, that is, does the drug prevent post-procedural events, then only events occurring after a revascularization procedure will be considered.

And finally, of course, it's important to evaluate whether or not there is a drug effect in the absence of revascularization and these groups of patients will be assessed as well.

Focusing first then on the strategy of

percutaneous revascularization within the first 72 hours, this time to event curve shows the rates of death and myocardial infarction in the two treatment groups. Eptifibatide therapy reduced this composite endpoint from 16.8 to 11.8 percent at 30 days, an absolute five point reduction in this endpoint representing a 30 percent relative risk reduction.

Interestingly, the shape of the curve, that is, the early rise toward the -- or the clustering of events in the very early time periods can be contrasted later on to similar curves for the patients who did not receive intervention, but one can see that the events occurred particularly early, that is, were clustered around the interventional procedure.

Expressing in terms of odds ratios at the three prespecified time points, 96 hours, seven days and 30 days, it is clear that the absolute difference of five percentage points occurred very early, that is, within the first 96 hours, and was maintained representing relative treatment differences of 30 to 40 percent over those time periods.

Now, this includes all endpoint myocardial infarctions, including those occurring prior to the performance of the intervention, that is, including the beneficial protective effect or stabilization

effect allowing the intervention to be carried out.

If instead we focus on the procedural-related events that were affected by the drug, this odds ratio plot focuses or includes only myocardial infarctions occurring after initiation of the procedure. One can see that at 30 days the difference was 12.6 percent of the placebo group versus 10.3 percent in the Integrilin group, a difference of 2.3 absolute percentage points. That difference was achieved early and maintained throughout the time period, a relative risk reduction of approximately 25 percent at 30 days.

Now, of the 1,228 patients in the overall trial treated within the first 72 hours, notably, 921 or three quarters were treated within North America. That is the majority of the early procedures, three quarters were carried out in the North American region, that is, the United States and Canada, actually, primarily, the United States.

This subgroup is most relevant in terms of comparison to the IMPACT II trial, which was a North American trial, and so I will also present data specifically for the North American patients, who do represent the majority of the patients undergoing early intervention.

Among those 921 patients, looking at the strategy of coronary intervention, that's including all infarctions, including those prior to the interventional procedure, we see a difference from 16.5 to 11.6 percent, again, almost a five percent absolute point difference at 30 days, achieved early, maintained throughout the time period, approximately 30 to 40 percent relative risk reduction.

Looking mechanistically at the angioplasty-related events only, a difference from 12.7 to 10.1 percent if we include only infarctions occurring after initiation of the procedure, an absolute 2.6 percent difference achieved early again and maintained throughout the time period, again, approximately 25 percent relative risk reduction in the North American patients, looking at post-procedural events.

Amongst glycoprotein IIb/IIIa receptor trials, the PURSUIT trial is one of the few to include a fair number of patients who underwent stenting, as elective stenting was common during this time period, a total of 600 patients, somewhat over 600 patients received stents during that early time period, and another almost 600 did not. Many of these stents were elective stent procedures. The treatment effect of eptifibatide therapy at each of the three time points

for stented patients versus patients who did not receive stents is shown in these two graphs, and as one can see, the treatment effect of eptifibatide appears to be present regardless of the choice of the modality of percutaneous revascularization.

This slide summarizes the risk, the bleeding risk, in the early intervention group of patients, and contrasts it for comparison and for perspective to the IMPACT II trial.

Focusing first on the right-hand side of the slide, this is major bleeding as defined by the TIMI criteria among patients, only those who underwent early intervention, but excluding bleeding related to coronary bypass graft surgery. This bleeding rate was increased from 1.1 percent in the placebo group to 4.3 percent in the eptifibatide treatment group.

For comparison, that rate was increased from 1.7 to 2.7 percent in the IMPACT II trial. Now, this does appear to be a somewhat increased gradient of bleeding risk with eptifibatide in PURSUIT relative to IMPACT II, but such a comparison can only be made with several caveats, recognizing first that the study drug therapy was at least 72 hours in PURSUIT, compared to 24 hours in IMPACT II, Heparin therapy was much less regulated and much more prolonged in

PURSUIT, relative to IMPACT II, the patient populations were substantially different with older, lighter weight and female patients, much more represented in PURSUIT rather than IMPACT II, and the expertise of the treating centers was much greater and the familiarity with IIb/IIIa blockade in the IMPACT II trial as compared to the global PURSUIT trial.

Moving on now to the question of whether or not eptifibatide therapy also has benefit in the patients who did not undergo percutaneous revascularization, we have time to event rates among patients who did not undergo revascularization or among patients who were revascularized but were censored at the time of revascularization. And, for this slide, revascularization is defined as percutaneous as well as surgical revascularization, and since it is censored at the time of intervention is not confined to early revascularization.

Now, what this analysis does, therefore, is focus only on events that are prevented by therapy before a revascularization procedure is carried out or in the absence of a revascularization procedure.

The event rate then at 30 days was diminished from 16.5 to 14.9 percent by eptifibatide therapy, an absolute 1.6 percentage point difference.

I will remind you that that 1.6 percent percentage difference, or approximately ten percent relative difference, is equivalent in magnitude to the overall treatment effect in the PURSUIT trial overall, so this is not a trivial benefit.

It is, perhaps, relevant, however, to compare the magnitude of the treatment effect of eptifibatide among patients who did undergo early intervention, that is, within the first 72 hours as compared to those who did not undergo early intervention, not to establish whether or not treatment effect exists, because it does exist for both groups of patients, but, perhaps, to get a feel for the magnitude of the treatment effect.

As one can see here, for the entire population in the world, that is, 1,200 patients undergoing coronary intervention, as compared to those who did not, the magnitude of the treatment effect does appear to be somewhat greater among those patients who did undergo coronary intervention than among those who did not. But, interestingly, in North America, again, constituting three quarters of the early interventions, that difference between the treatment effect with or without coronary intervention was much less pronounced, and, clearly, both groups of

patients did enjoy a substantial benefit with eptifibatide therapy, regardless of their early interventional status.

Again, we caution that this is a subgroup analysis of a post-randomization event, no statistical inferences can or were attempted to be drawn, and we regarded these findings as observational, rather than the product of a properly randomized analysis.

Within those constraints, it is apparent that the treatment effect of eptifibatide therapy was observed in patients who did or among those who did not undergo early revascularization, that is, during the first 72 hours on study drug therapy. There was, apparently, at least worldwide, a trend toward somewhat greater treatment effect when eptifibatide was administered to percutaneous revascularization procedures.

These findings are supportive of the biological mechanism of action of eptifibatide, and its effect on platelet mediated events occurring in patients who undergo either induced or spontaneous plaque rupture with consistency with the findings of the earlier study confined to patients with induced plaque rupture.

Thank you very much.

CHAIRPERSON PARKER: Do we have any questions from the committee, specifically, on Doctor Lincoff's presentation?

Dan?

DOCTOR RODEN: I guess I'd like to know are there other patient characteristics that have been looked at to try to explain the difference in outcome between North America and the rest of the world, you focused on the use of interventions, I have specific questions with regard to concomitant medication use, specifically, Heparin, Aspirin, ACE inhibitors, beta blockers?

DOCTOR LINCOFF: Do we have the slides of the multivariate analysis that looked --

DOCTOR HARRINGTON: Can we have slide 31, please, and we can go through smoking.

DOCTOR RODEN: Okay.

DOCTOR HARRINGTON: What you see on this slide is the ACE inhibitor use, the beta blocker use, the calcium channel blocker use, and there's balance between the treatment groups, but we'll point ACE inhibitors highest usage in Eastern Europe, as I alluded to in my talk, at the time of entry into the trial the history of heart failure is 20 percent in Eastern Europe versus 10 ten percent in the other

three regions. Beta blocker use, pretty consistent in the top three regions, a bit less in Latin America, though the Latin American was the smallest region in terms of population. Calcium channel blocker use, lowest in Eastern Europe in the mid to high 30s in the other three regions.

Can we have the baseline characteristics, what slide is this, Michael? Could I have this slide?

With regard to some of the comments I've made, you can see heart failure, this is as reported by the patient to the physician, there did not need to be any documentation of heart failure, but as self-reported by the patient to the physician 11 percent North America, nine percent Western Europe, six percent Latin America, 20 percent in Eastern Europe, and we'll get you the smoking data in a moment.

Could I have slide two? This gives you the breakdown of males and females. As I've pointed out, approximately a third of the population in North America, Western Europe and Latin America are female, and almost 50 percent in Eastern Europe, and could I have slide six? This is the overall smoking, with 28 percent, this is current smokers in the overall population, to try to get to your question, Doctor Roden, three of the regions were very close, all in

the low 30s, the exception was Eastern Europe where self-reported smoking was 19 percent in that region.

So, this is self-reported smoking.

DOCTOR KONSTAM: Was there a difference in the age distributions across the regions?

DOCTOR HARRINGTON: The age distribution we can show you, I need the age distribution by region. Could I have slide two? These are the mean ages, North America 62, 63, 63, a little lower in Latin America, 59.

CHAIRPERSON PARKER: John?

DOCTOR DiMARCO: In IMPACT II, there were some protocol described times for drawing CKs, was there any description for people who had interventions where CKs were routinely drawn again, or were all these clinical events, or were they just drawn by local practice, it was sort of random when people got CKs if they had a percutaneous event.

DOCTOR LINCOFF: Following procedures, they were specified in the same schedule.

DOCTOR DiMARCO: So that, so could you tell me, so any time someone had a percutaneous intervention they had CKs drawn at eight, 16 and 24 hours?

DOCTOR LINCOFF: Yes, similarly, if they

had a bypass surgical procedure.

CHAIRPERSON PARKER: Anyone else on the committee have any questions?

DOCTOR LINDENFELD: Maybe I just have one question. You showed us data, you didn't, but earlier we saw data about the number of large infarcts greater than five times CK, is there a difference in the total number of infarcts that were just enzyme infarcts post-intervention? Is there a large difference there in the percentage?

DOCTOR LINCOFF: Oh, I don't have the breakdown specifically in the post-intervention patients of the infarct sizes.

DOCTOR HARRINGTON: The only thing I'd point out is that the definition of infarction in the post angioplasty state required a CKMB elevation three times the upper limit of normal. So, the definition of infarction was tailored to the early enrollment infarction, the non-interventional infarction, the PTCA infarction, which was three times the upper limit of normal, or the post-CABG infarction, which was five times the upper limit of normal.

So, with that caveat, no, we've not broken down the post PTCA infarcts into three, five, seven, ten yet, but the minimum was three times the upper

limit of normal.

DOCTOR LINDENFELD: But, there were a larger number of non-clinical we detected infarcts in that group?

DOCTOR HARRINGTON: We've not broken that down yet.

DOCTOR LINDENFELD: Likely there were, though.

DOCTOR HARRINGTON: Like we have in other than the overall that you've seen.

CHAIRPERSON PARKER: Anyone else on the committee have any questions?

JoAnn?

DOCTOR LINDENFELD: I have one. This isn't specifically about the regional variation, but we saw data earlier that there were about, I think, around 14 events, say, per 1,000 patients treated or 14 events prevented, if we then put into that equation the number of transfusions that were given and subtract it, how many events do we have per thousand patients treated? It would be about one or two, is that correct?

DOCTOR HARRINGTON: The absolute increase in transfusion, as you've alluded to, is similar to the absolute benefit of prevention of MI. The caveat

there would be comparing the irreversible complication of death and myocardial infarction to the more temporary, though important, transfusion indication. So, yes, if you did that analysis you would take away much of the absolute benefit.

In previous trials, we've used the term net clinical benefit to refer to prevention of death, myocardial infarction and add in stroke. If you do that, the net clinical benefit does not change, but you are correct, it changes the other way.

DOCTOR LINDENFELD: Well, I think we all agree that those are important endpoints. I just -- and we have data now that even these small infarcts are probably important, but I don't know that we have any data, maybe you do, about what the effect of transfusion is on long-term outcome? Can we be sure that that's not an important clinical event?

DOCTOR HARRINGTON: I agree that it's definitely an important clinical event, but we do not have the long-term data on that, you are correct.

DOCTOR PIÑA: Milton, I just have one last question.

Do you have any data on the timing from symptom onset to the presentation at the center per country? I am trying in my own mind to see the

differences, I see the interventional differences within the different parts of the world, what about presentation, do you have any data on that?

DOCTOR LINCOFF: I don't know if we have the timing slide here. I don't think we have the data here.

DOCTOR HARRINGTON: Can I have slide 88? This gives it to you, the overall population, looking at the treatment effect based upon the time that you presented. We don't have it broken down by region. The median time to presentation from the onset of the index event to the time of randomization was 11 hours.

DOCTOR KITT: It was not appreciably different between the regions, or among the regions, and I don't have that to show you.

This looks at the treatment effect by the time of presentation.

DOCTOR LINDENFELD: Now, just a follow up, maybe I missed it, but did you tell us what percentage of women had an intervention, the overall was around 20 to 23 percent, because there was this gender difference in effect.

DOCTOR LINCOFF: Yes, we have a slide by gender. Do we have the slide by gender? That's a very complicated one. Do you want overall or by

region?

DOCTOR LINDENFELD: Either one.

DOCTOR LINCOFF: Okay, by region, 29, please. PTCA timing by region and gender, yes, 29. All right. What this slide shows is males in the white box, females in the green, at each of the three prespecified time points, which actually is 96 hours, seven days and 30 days, in the four regions, North America, Western Europe, Eastern Europe and Latin America, and then overall.

The general trend here is that the women underwent intervention at each of the time points less frequently than did men, but there are not clear regional differences in that. That is, even in North America, there was a pattern of each time point that women underwent intervention less frequently than men, certainly in Western Europe, Eastern Europe and Latin America.

Now, when these overall intervention rates are low you can say proportionately this difference is more, but the overall gestalt here is that the women underwent intervention less frequently than men did at each time point in each of the four geographic regions, and the difference is about 20 percent.

CHAIRPERSON PARKER: Does the committee

have any other questions?

DOCTOR LINCOFF: Okay. Then, Doctor Kitt will come back --

DOCTOR RODEN: I have one question.

CHAIRPERSON PARKER: Dan?

DOCTOR RODEN: I forgot to ask this the last time we met, and I want to ask it this time. Are there any other trials that are ongoing with eptifibatide?

DOCTOR KITT: Had you asked that the last time we'd have told you PURSUIT and PRIDE, both of those have been reported, but at this time we have no other ongoing, actively enrolling ongoing trials with the exception of a very early phase study going on in Japan.

CHAIRPERSON PARKER: Any other questions of the committee?

Doctor Kitt, will you summarize before we break?

DOCTOR KITT: I did want to mention before I started my summary that there was extensive information presented to the committee one year ago that was in the briefing book that is not available to you at this time, but the totality of the data was very important to present for the IMPACT II study, and

I just wanted to be sure that that point was made.

I wanted to, if you'd like, to respond to two questions where I said I'd come back and give you some data, if you'd like, and one was, you had asked about the six-month data, and what the p value would be for death and MI. For the 135.5 it was .2, and for the 135.7 it was .3.

And, the second question you asked me was about the pooled analysis. We had specifically not pooled the analysis in the IMPACT II study between the two doses, specifically because of the pairwise comparisons. However, we were asked to pool all of the data available at the time between IMPACT II and IMPACT I, so if I could have the back-up slide 380, I could show you the results, which, again, are very consistent with the overall IMPACT II and angioplasty experience, looking at now an additional 150 patients added from IMPACT II.

In this experience, you see that the treatment differences remain still about the same, 2.2 percent absolute reduction, and the p value, once again, even combining the two doses and another study.

CHAIRPERSON PARKER: What's the endpoint?

DOCTOR KITT: The endpoints are death, MI --- intervention.

CHAIRPERSON PARKER: But, the intervention was not measured in PURSUIT.

DOCTOR KITT: Right, this is not with PURSUIT, this is IMPACT and IMPACT II.

CHAIRPERSON PARKER: Oh.

DOCTOR KITT: The last point I wanted to make as we were leaving is, again, both treated as randomized and the randomized patient analyses were prespecified in both studies, and we specifically, as we discussed in detail the last time we were here, thought that the most logical analysis for IMPACT II was the treated as randomized patient analysis because of this issue of not -- the patients who were being randomized in IMPACT II were having their randomization occur before -- frequently before they got into the cath lab, before the original scout film was done in the lab, and several decisions were made subsequent to that decision that would not introduce bias, and that was the reason why we chose that as our primary analysis, although we have both analyses presented in both studies.

So, can I have my last slide, please?

In development plans for Integrilin, COR viewed the two indications studied, namely, unstable angina and non Q-wave myocardial infarction, and the

prevention of acute ischemic events in patients undergoing coronary angioplasty as complimentary.

Efficacy in each of these clinical settings supporting the common pathophysiology of intracoronary thrombus formation and its prevention by inhibition of platelet GP IIb/IIIa.

We have presented the results of two studies, the IMPACT II study and the PURSUIT studies. They are both large, well-controlled studies which demonstrate the efficacy and safety of Integrilin in these two closely related clinical settings.

Both of these studies have demonstrated a benefit of treatment on the irreversible clinical endpoints of death and myocardial infarction with an acceptable safety profile.

We have also pointed out that there is considerable overlap in the patient populations and treatment strategies. Patients in PURSUIT underwent coronary angioplasty and patients with unstable angina were enrolled in the IMPACT II study.

In addition, these two clinical settings were specifically referred to in an FDA draft guidance document which is included in your briefing document, and which it is noted, "because the endpoint studied and the theoretical basis for use of an antithrombotic

agent are suitably similar, each study supports the other for each claim."

Finally, although the dosing regimens in the two studies were different, we have pointed out that the PURSUIT dosing regimen of 180 2.0 consistently achieved a pharmacodynamic target during the entire treatment period, whereas, this was only achieved after the bolus dose in the IMPACT II study.

We've demonstrated that this dose can provide benefit with a favorable risk to benefit ratio. We are, therefore, recommending that the dosing regimen studied in patients with unstable angina, non Q-wave myocardial infarction be the same as in patients undergoing coronary angioplasty.

I would like to thank the FDA for their rapid review of the amendment to our NDA and would be happy to entertain any other questions at this time.

CHAIRPERSON PARKER: JoAnn?

DOCTOR LINDENFELD: Just as I understand it, 30 days both studies had about a 1.5 percent absolute benefit, and if that's correct then why recommend the higher dose that has more bleeding?

DOCTOR KITT: Well, that would only be true if we were comparing the two populations identically, but they are not identical. As Doctor Lincoff pointed

out, if you try to compare similar populations, in other words, patients in PURSUIT who underwent coronary angioplasty, it was about a four percent absolute decrease in the incidence of death and MI, compared to, as you said, about a 1-1/2 percent in IMPACT II.

But, again, these comparisons are difficult because, again, very different treatment management strategies between the two studies.

CHAIRPERSON PARKER: Any other questions?

If not, we will break. We need to reconvene at 1:15. We will reconvene at 1:15, because we need to proceed with the questions in an expedited fashion.

(Whereupon, the meeting was recessed at 12:50 p.m., to reconvene at 1:15 p.m., this same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:28 p.m.

CHAIRPERSON PARKER: I'd ask people to take their seats, please. We will begin this afternoon's session with the discussions of the questions. The Advisory Committee is being asked to consider the evidence provided by two major clinical trials, IMPACT II and PURSUIT, and is being asked to consider each trial separately and then to consider whether they support one another.

In a draft proposal on the evidence needed to support marketing, the Agency specifically suggested that the regulatory requirement for independent substantiation for an antiplatelet agent could be met by two studies, one in a post-angioplasty setting and the other in the acute coronary syndrome, because these settings share some pathophysiologic basis. Therefore, the draft proposal says that two such studies would support use in both clinical settings.

Now, the first series of questions deals with the committee's deliberations on IMPACT II alone. We will skip questions one and two, and proceed to question three. Do the results of IMPACT II alone demonstrate a treatment effect of Integrilin when used

as adjunctive therapy in patients undergoing PTCA? That is the first question, and depending on the answers to those questions we may or may not need to go on to the sub-questions.

We'll begin with the committee reviewer. John?

DOCTOR DiMARCO: Well, I must admit I'm a little concerned that the investigators in their papers said that there was no difference in IMPACT II between -- or statistically significant difference, but I think I will stand on the committee's opinion from last year that there wasn't a drug effect that just achieved statistical significance in IMPACT II, so that I did think there was a beneficial effective treatment.

Do you want me to go on to the effective dose?

CHAIRPERSON PARKER: Not yet, because what we need to do is to have a -- depending on how the committee votes in general, one would go to the sub-questions.

DOCTOR DiMARCO: Okay.

CHAIRPERSON PARKER: General discussion?

DOCTOR KONSTAM: Just in terms of clarification, is the question asking whether we think

IMPACT II is positive, or is the question asking whether IMPACT II is sufficient for approvability?

CHAIRPERSON PARKER: I don't think that it has anything to do with IMPACT II being sufficient for approvability, if I understand it correctly, Ray. I think the question here is whether IMPACT II alone demonstrates that the drug is effective.

DOCTOR KONSTAM: Is it a positive --

DOCTOR LIPICKY: Well, you'll notice that that word is explicitly not expressed.

CHAIRPERSON PARKER: The word effective.

DOCTOR LIPICKY: Positive.

CHAIRPERSON PARKER: Right.

DOCTOR LIPICKY: The question is, do you think that there was a beneficial treatment effect shown, and then just to anticipate how the rest of the discussion may go, it would be how convincing was it and is that convincing enough to be approved on that basis, and I still repeat the statement I made about five hours ago, I guess, that the wrong thing to do is to look for two check marks in two boxes that say trial one positive, yes/no, and trial two positive, yes/no. It is strength of evidence that supports approval. The only binary decision you need to make here today is whether it is approvable or not

approvable. The rest of it is how convinced you are that there is an effect, and where that effect may be.

So, this is the first question that starts deal with that.

CHAIRPERSON PARKER: I understand that that's a response which is slightly different than the kind of response we generally think about, but I think that there is a -- I think Ray is asking us specifically not to consider the concept of positive versus negative. I think that the problem is we generally think of life in binary ways.

DOCTOR LIPICKY: I realize that, Milton, I don't think it's appropriate.

DOCTOR MOYÉ: Ray, let me ask a question.

CHAIRPERSON PARKER: Lem?

DOCTOR MOYÉ: Ray, let me ask you specifically, typically and traditionally, we are concerned about the strength of evidence from clinical trials. There's nothing new there.

We often encapsulate that in the notion of whether the trial is positive or not. Now, I think you've been a strong supporter of that, if my memory is clear. Maybe my memory is not clear. Now, are you asking us to disregard that issue today?

DOCTOR LIPICKY: No. Geez, I really don't

want to make this be long, but I do want you to make decisions on the basis of data, and I do want you to make decisions on the basis of some kind of statistical treatment of the data. I think that it is becoming increasingly clear, and this will be the first time it's, I guess, discussed and that may have been an error to introduce today, that the .05 thing is really not a holy grail, it's a convention, and that approvals generally are at .05 squared divided by two, right? So that, the strength of evidence that is required to say something should be introduced for therapy, put in those terms, and those are not the only terms they should be viewed from, are that kind of strength of evidence, and it doesn't have to come on the basis of having trials be positive and positive, okay, nor as the guidelines say does it have to be in the identical patient population in order to be able to draw a conclusion.

It is still strength of evidence, the strength of evidence still comes from statistical evaluation, but it is not -- and one still has to make the decision, is the trial result a table of random numbers, you still have to make that decision. So, I'm not departing from that view, but I don't want it to be a check box in two of .05, because that, I don't

think, is the proper exercise.

CHAIRPERSON PARKER: But, if you want to make it that, you may.

I think that this is relatively new territory for us, because the conventional way -- it is not that we think, nor should we think, that a trial with a p value of .08 demonstrated nothing, and I think that it is not clear that a trial with a p value of .08 should be considered to be less persuasive than a trial with a p value of .049, because I think we would be -- many would hasten to remind us that the effect is borderline regardless on which side of the .05 critical line the p value tends to occur, and depending on how you do the analysis we can appear on either side of the line.

The fact is that we spend an enormous amount of time arguing over about where that p value is, I mean, we spent a lot of time this morning on that, a lot of the questions are on that, God, you know, why would we spend all this time if it didn't matter?

DOCTOR LIPICKY: Well, because I wasn't sure that you would buy the statement I just made about how you should look at this, and I wanted to be prepared in either event.

CHAIRPERSON PARKER: There's some days when you wake up in the morning and you know it's going to be that kind of day.

I think that the committee probably has an idea of what Ray is trying to say, and I guess we need to -- I think probably the best thing, Ray, is to really allow for an elucidation of this. It's probably a good thing to respond to question three, since you don't want us to think binarily, we should not respond as a yes or no. What we should do is describe what we think IMPACT II found, because that's the only way of describing to you what we think about it. In other words, we can't give you a binary answer if you don't want us to think binarily.

DOCTOR LIPICKY: Well, I must admit you have me there, Milton.

CHAIRPERSON PARKER: Okay.

Then, John, the question -- I think actually you have already answered the question, but I think that what we need to do as a committee is to not necessarily consider yes or no, but to simply state our opinion about IMPACT II and what conclusions or feelings we have about IMPACT II, and I think that's probably the best way of doing it.

Bob?

DOCTOR FENICHEL: Yes. Milton, maybe it would be helpful to the committee if some of the discussion now were recast along the lines that were used in October at the meeting when we discussed Clopidadril, and there members of the committee will recall that there were several different assertions put forward saying, well, this trial seemed to show this, or some might say this trial showed this assertion.

And then the members of the committee were asked, well, do you think, no, it didn't show that at all, that's a misinterpretation, I mean you couldn't begin to draw that conclusion, you really are at ground zero with respect to that assertion, at square zero I should say, then the other thing you say, well, yes, it sort of supports that view, but it's not even as strong as we think an ordinary .05 sort of trial is, or, yes, you know, that's at least as strong as two .05 trials, that by itself carries the day with respect to that assertion.

So, the idea was, if one said, as one might say with response to this question, well, no, IMPACT doesn't really prove that's it, you know, it's not probably the last word, which is what, of course, the committee said last year with respect to IMPACT II,

that this does not package the whole thing up, but you might then be able to say, well, what it would take is such and such, meaning for one thing you might say, well, IMPACT II was just worthless, it was a waste of time, it was going to take two trials to get from here, which is no where, to approval. Or, you might say, well, IMPACT II was pretty good, it was like one trial, or maybe a little bit worse, or maybe a little bit better, whatever the committee chooses to say, this is how much it will take to get to an affirmative statement with respect to the thing.

I think that was a useful mode of discussion in October.

CHAIRPERSON PARKER: I think it worked in October, and I think it would be useful here, so let's just try to make it as simple as possible, is your view of IMPACT II that, (1) it didn't show anything, that's choice number one; (2) it was -- it provided evidence that indicated the likelihood of a treatment effect, but the strength of evidence was less than one usually sees in a single trial, equivalent to what one sees in a single trial, or equivalent to what one sees in two trials, in the conventional levels of significance. That's an adaptation of the sort of Clopidadril model, so the four levels are nothing,

less than one trial, one trial or two trials.

John?

DOCTOR DiMARCO: I was going to just say yes, but I regard IMPACT II as a single trial that would require confirmation.

CHAIRPERSON PARKER: Okay.

Discussion in general before a vote?

Okay, Lem?

DOCTOR MOYÉ: I think that IMPACT II showed a tendency to benefit. However, I think that the information for effect, statistical reliability of the effect, whether the effect would be seen not just in a sample but in the population at large is very weak, and I think it's weak because the investigators, even though they had set up, admirably had set up prospectively a level of evidence, I won't say p value, I'll just say level of evidence, that suggests that the findings would not be due just to chance alone in the population, in fact, the analysis, from my point of view, was somewhat tainted by the fact that they did not do a true to the heart intention to treat analysis.

When the ITT analysis is done, it turns out that the strength of evidence is quite a bit weaker, so I think the evidence in IMPACT II is less than I

would see in one trial.

CHAIRPERSON PARKER: JoAnn?

DOCTOR LINDENFELD: I think the evidence -- I pretty much think what we thought in February, that the evidence is one good trial, one weak good trial.

CHAIRPERSON PARKER: Marv?

DOCTOR KONSTAM: Just for the sake of simplicity, I'm going to say that it is equivalent to one trial. I think that's what we did say the last time around, I accept the fact that the statistics are marginal, but, again, I'm going to come down saying I'll accept it as one trial.

CHAIRPERSON PARKER: Ileana?

DOCTOR PIÑA: I will also accept that it is one trial, with the caveat that the statistics don't satisfy me, as Lem has stated.

CHAIRPERSON PARKER: Dan?

DOCTOR RODEN: Well, I think if there were two IMPACT trials then they would -- I'm not sure that would be sufficient, so I'm going to come down with Lem, it's sort of less than one, but I could just as easily vote with everyone else at one with all the caveats that have been introduced.

CHAIRPERSON PARKER: My vote is less than one, I guess I'm concerned about the randomized

intention to treat analysis and some of the other issues that were brought up today, and think that there's definitely an indication that the drug did something, but I think the strength of the evidence is less than what one sees in a conventional trial.

So, the vote on that was 4:3, four being equivalent to and three being weaker than the usual one trial.

John, why don't you then take 3.1, 2 and 3 all at once. What is the effective dose, are the demonstrated -- et cetera, et cetera.

DOCTOR DiMARCO: I think dose is pretty easy. They are, essentially, indistinguishable, so I don't think we can say much about dose here. It would have helped me a little bit, since the proposal today is to go with a higher dose, if the orders had been reversed, even though they still would be indistinguishable, but I don't think we can distinguish between the two doses that were used in that trial.

The demonstrated incidence in severity of bleeding in that patient population I think was acceptable and in line with what you'd expect for an agent that affects platelet functioning, people undergoing interventions, and I would not consider, as

I said before, this actually we get to -- you have to answer this one binary function --

CHAIRPERSON PARKER: Yes.

DOCTOR DiMARCO: -- I would say that, as I still agree with the February decision, that I would not approve it just on that basis.

CHAIRPERSON PARKER: Does anyone on the committee disagree with John's votes and conclusions here? Basically -- yes, Dan?

DOCTOR RODEN: I don't disagree, I just want to say that it seems to me the lesson to be taken away from this for anyone else in the audience is that the homework needs to be done before the megatrials are mounted, that it's awesome to me that a megatrial of this size was mounted without people knowing what the right dose is, and we still don't know what the right dose is.

CHAIRPERSON PARKER: JoAnn?

DOCTOR LINDENFELD: I agree with that, but I just want to bring up one other point that I missed before, and I'm sorry to go back, but my reading of IMPACT II is that, actually, there was no benefit in women, and, in fact, if anything it tended toward being adversely -- toward adversely affecting women, is that correct? I'm concerned about this only

because of the results we've seen in PURSUIT.

DOCTOR KITT: Can I have slide 359 on the back-up? In actuality, there was an effect in women, and death, if you look at death, MI and urgent intervention there's very little difference, but in death and MI alone there's actually a considerable amount of benefit.

This is death and MI by gender in males, looking at the placebo group, the 135.5, 135.75 and combined, and you can see from 8.2 to 6.8, 8.2 to 7.3, in women 9.1 to 7.1, 9.1 to 7.2, so, in fact, there was evidence in IMPACT II of a benefit.

DOCTOR DiMARCO: Can you show us the data with urgent interventions in there, too, since that was your endpoint?

DOCTOR KITT: 365, please. These are the results looking at the death, MI and urgent intervention. Again, these are the primary results in males, 11.6 to 8.5 or 9.9, in women, 11.4 to 10.1 -- 10.6 and 10.1, so less of an effect, obviously, in urgent intervention.

CHAIRPERSON PARKER: JoAnn, do you have any follow up on this?

DOCTOR LINDENFELD: No, that's what I needed.

CHAIRPERSON PARKER: Next series of questions focuses on PURSUIT, question number four, the PURSUIT results were geographically heterogenous with respect to both magnitude and direction of treatment effect. Does this fact, (1) strengthen one's confidence in the inferences drawn from the study; (2) undermine one's confidence in the inferences drawn from the study; or, play no role in interpreting the study?

John?

DOCTOR DiMARCO: Well, I think that this is hard to address just in terms of geography, because as the sponsor has presented, the practice patterns in the various areas were considerably different, and the patient populations were somewhat different in the various areas. And, in particular, since we've already said -- or, I've already said that I think that there are some reasonable data showing benefit in a population that's undergoing intervention, and a lot of the intervention occurred in the geographical area that showed the most benefit, I think that I am not as struck by the geographic variation as in the practice variation. So, I don't think geography, per se, is influencing me, but I think the practice pattern is going to be influencing my opinions.

CHAIRPERSON PARKER: So, your selection here is?

DOCTOR DiMARCO: It's hard to say. Really, geography, per se, played no role.

CHAIRPERSON PARKER: You can substitute whatever you want for geography.

DOCTOR DiMARCO: Yes, I will substitute, I say geography isn't the factor, it's practice pattern.

CHAIRPERSON PARKER: So, does the different practice patterns that is evidence from the studies alter anything about what you want to conclude?

DOCTOR DiMARCO: Yes, I think that it looks pretty clear to me that most of the benefit was early on, and the biggest benefit was in people who had an intervention.

DOCTOR LIPICKY: But, that has nothing to do with the question.

CHAIRPERSON PARKER: Would it be correct to say that your answer is that it doesn't play a role in your interpretation?

DOCTOR LIPICKY: Well, from his answer that's what I would infer, but that's not what he said.

DOCTOR LINDENFELD: Well, it could play a role if you assume that the inference is that --

DOCTOR DiMARCO: You may have -- it depends on what inferences you are taking, my inference is that most of the benefit was seen in people who had interventions.

DOCTOR LIPICKY: No, this is really inference from the trial as a whole. You are going to draw some conclusion about what you think the trial showed.

DOCTOR DiMARCO: Well, tell me which inference you want me to say is strengthened, or my inference for the trial is that most of the benefit was seen in the people who had an intervention.

DOCTOR KONSTAM: Can I clarify what --

DOCTOR DiMARCO: If you will.

DOCTOR KONSTAM: I'm sorry, well, I just was going to ask Ray, are you asking, does the geographic heterogeneity alter your view of the strength of the overall finding of the study? Is that the question?

DOCTOR LIPICKY: Correct, that's a better way of putting it.

DOCTOR KONSTAM: Right, does it alter your overall view of whether it was a positive study or not.

DOCTOR LIPICKY: Correct.

Well, no, I'd rather you hadn't used that word.

CHAIRPERSON PARKER: Maybe the best way is, does the fact that the findings appear to be geographically heterogenous, is it a cause of concern? No, that won't help.

DOCTOR DiMARCO: Maybe it's -- Ray, are you asking that, do I feel that the geographic or the practice pattern change affects the conclusion that the study was positive in all comers with unstable angina or non Q-wave myocardial infarction?

DOCTOR LIPICKY: Yes, I guess that's right, and I think, once again, from all of the answers that you have been giving --

DOCTOR DiMARCO: Then I would say it undermines my confidence, that it's widely applicable to that population.

DOCTOR LIPICKY: Okay.

CHAIRPERSON PARKER: Okay.

Let's see, we'll begin on the other end, Dan?

DOCTOR RODEN: I agree with John, I think it undermines one's confidence. In fact, when you look at all the data together, a good case could be made for the adjunctive use of eptifibatide --

CHAIRPERSON PARKER: Integrilin.

DOCTOR RODEN: -- I'm going to try hard to stay away from that, EP -- in procedures, and not much else.

I don't know if we are allowed to change the indications.

DOCTOR LIPICKY: No, that's okay.

CHAIRPERSON PARKER: Okay.

So, I think it's two votes for undermines. Okay.

Ileana?

DOCTOR PIÑA: So, three votes for undermines.

CHAIRPERSON PARKER: Marv?

DOCTOR KONSTAM: I'm going to say no impact. I guess I'd put it more clearly by saying that it undermines it by a little enough margin that I'm going to say no impact.

And, I think there seems to me to be something going on with regard to this heterogeneity, and I think that's just, you know, a second to what John said. It's not clear to me at all what precisely that is, or my gestalt is that it's, in fact, multifactorial, and not purely associated with the difference in the interventions.

But, if anything, I think, since we are going to head toward the issue of approvability in the United States, I think, if anything, the strength of the finding was strongest among people entered in the United States.

So, I'm going to wind up saying that --

CHAIRPERSON PARKER: Well, Marv, Marv, really, you actually want to link those two?

DOCTOR KONSTAM: Which two?

CHAIRPERSON PARKER: Just think about it, just suppose that the heterogeneity was that this drug was better in Eastern Europe and Latin America, and that the findings in the United States look like they did in Eastern Europe because this Advisory Committee meeting is taking place in Maryland you would say that -- that doesn't make sense.

DOCTOR KONSTAM: Doctor Packer, let me say clearly what I said in the beginning, is that I am concerned little enough with the heterogeneity that I do not believe that the heterogeneity undermines my overall interpretation of the finding, and that's the most important part of my answer.

The other thing I was going to say is, part of my explanation for that, of my lack of being undermined, is the ends across these various

geographic areas is another point to be made. So, it doesn't undermine my view of the overall trial.

DOCTOR LINDENFELD: Yes, this doesn't undermine my overall view of the trial, but I think what it does undermine is my conviction that this is a treatment across the board maybe for everyone with unstable angina and non Q-wave infarct.

DOCTOR MOYÉ: It really plays no role for me in drawing inferences. The heterogeneity in subgroup analysis bedevils us in clinical trials. It's almost impossible to interpret reliably.

We are best guided, in my view we are best guided by the findings for the primary endpoint in the total cohort, so it doesn't play any role in drawing inferences for me from the study.

CHAIRPERSON PARKER: And, my vote is that it does not undermine my confidence either, so I guess a very split vote, four no undermine, and three undermine, just for the record.

The next question, which is five, pertains to statistical issues related to interim analyses. Number one, what prospective rules were established in conducting such analyses and controlling for the overall type 1 error as a result of them.

Lem, we'll look towards you to lead us off

on this.

DOCTOR MOYÉ: Sure.

I can go through these one after another, if you'd like.

CHAIRPERSON PARKER: Why don't you do that, that would be great.

DOCTOR MOYÉ: Okay. We had a lot of discussion about it this morning.

There were prospective rules established for conducting the analyses. The prospective rules were based on a definition of what the endpoint was. They did not know exactly what two groups were going to be compared at the end of the trial when they were making the rules at the beginning, but they knew they were going to compare two and only two.

The data available to the parties performing the interim analysis depended on the purpose of the analyses. The safety data were available, mortality data was available for most of the analyses, and primary endpoint data were available for the primary endpoint interim analyses.

By my count, there were three interim analyses performed, and there was one preliminary analysis that was performed, not included as an interim analysis because it was an assessment of the

appropriateness of including patients who were at least 75 years of age in the study.

5.4, given the interim analyses actually performed, did the final analysis appropriately control for type 1 error? I think I have to disagree with the investigators here. I am very uncomfortable with this notion of making decisions during the interim analysis of a trial, and not accruing alpha. I am much more comfortable with the more traditional assertion that early decisions in the trial must be compensated for in the end with some adjustment of alpha. The investigators did not do that.

The FDA did do that, and I'm going to come down on the side of the FDA statisticians here.

5.5 changes tack somewhat, was there a prospective plan to consider discontinuation of the one of the active treatment arms? Yes, there was. Does the trial design preserve the type 1 error rate? Well, this is a little tricky. I have to say yes, though, because this really clearly is not just play the winner, they had decided that if they were going to allow both treatment arms to continue that they were going to test placebo versus high dose. So, I have to say that in that limited -- in the limited area of the question there was type 1 error rate

preservation here, vis-á-vis the two versus three treatment groups.

With respect to preservation of the interpretability of the trial, was an appropriate decision made to discontinue an arm? I think so. Is it appropriate for the final analysis to be a comparison of only the placebo and high dose arms? Here, I think that's correct as well, I would agree.

CHAIRPERSON PARKER: Okay.

Lem, thank you very much for going through all that. Is there anyone on the committee who would like to discuss or disagree with what Lem has said?

Okay, then it sounds as if the committee is concordant on all of the conclusions that Lem enunciated for question number five.

Joan, do we have all that? Okay, good.

Question number six, number six also is a series of questions pertaining to the primary endpoint, which is an unadjusted Chi Square analysis of the proportion of subjects in each group having death or myocardial infarction in the first 30 days.

I guess to be quite fair to the question, because otherwise the question doesn't work, we should modify the question to say that one should answer these questions based on the adjusted Chi Square

analysis, but given the fact that the conclusions reached are the same whether one penalizes or doesn't penalize, that is, whether the p value is .05 or .0478, then I think that we should answer the questions without getting into that issue again, because that issue was addressed in question five.

DOCTOR LIPICKY: I'm not really sure I followed all of that, but it sounds good.

CHAIRPERSON PARKER: Okay.

The first question, we'll turn back to John, is this a reasonable endpoint, which is death or MI in 30 days, for such a population, and if not, what is?

DOCTOR DiMARCO: I think it's a reasonable endpoint. It gives you a measure both of some intermediate term benefit, as well as picking up some early effect.

The question I think later comes up about what about time to first event, and I think that's a little more difficult because you'd have to --

CHAIRPERSON PARKER: No, no, I'm so sorry, we --

DOCTOR DiMARCO: We don't get that, so I think this is an acceptable endpoint.

CHAIRPERSON PARKER: Okay.

Basically, the endpoint, the elements of the endpoint, which are for discussion, is death or myocardial infarction at 30 days, as opposed to how you analyze that.

DOCTOR DiMARCO: I found it an acceptable endpoint.

CHAIRPERSON PARKER: Okay.

Discussion from the committee before we go around?

Let me ask the committee, I think death and Mi is a very conventional way of looking at events in this kind of population, because, you know, they are both irreversible, they are both serious, and we've had a lot of experience with that combined endpoint, and I think that combined endpoint probably more accurately portrays what's going on in this patient population than either alone.

I just want to know how comfortable the committee feels about 30 days. It's a pretty short time for a pretty serious event, and that is what the sponsor specified, but that is not what is being asked. We need to give credit to the sponsor for having specified 30 days, but what the Agency is asking us here is, in general, is this a good way to do things.

Dan?

DOCTOR RODEN: I mean, I think it's a compromise, in essence, isn't it, Milton, between the idea that the antiplatelet effects of the drug will be sort of most evident in reducing endpoints within the first several days, but the Agency is not all that interested in what happens in the first several days.

And, I guess if I were a patient, I'm not at all interested either if my overall survival to a week, or two weeks or three weeks is unaffected.

So, you'd like a very early endpoint, and then you'd like to know what happens to the patients after six months or something like that. So, I think the 30 days represents a reasonable compromise.

CHAIRPERSON PARKER: Okay.

DOCTOR LINDENFELD: Milton, this data was not non-fatal MI, it was just death and MI, so that death and MI would be counted twice if a patient died, if it was a non-fatal MI?

CHAIRPERSON PARKER: No. Right, it was death and non-fatal MI, they are not counted twice.

DOCTOR RODEN: I'm not sure that extending it longer helps. I mean, it may help in terms of the overall value of the procedure, but the problem is, you get so much noise if you go longer that it would

become very hard to demonstrate benefit, because, obviously, the effect of a drug, pharmacodynamic effect of the drug is going to be gone and then you are going to have all sorts of things happening in that next six-month period, so I think it's a reasonable thing to look at, but I think it would be hard to show it as a primary event.

CHAIRPERSON PARKER: Just so I understand, in thrombolytic agents, which are also given short term, in acute ischemic syndromes, well, specifically, MI, but part of the ischemic spectrum, we see the effect that is seen early persists long term almost invariably. Do you think that that's just not a standard that applies to this kind of agent?

Remember the concept here isn't angioplasty, it's unstable angina and/or non Q-wave MI, and when thrombolytics are given to Q-wave MI we see the effect persist, and we actually like to see that effect persist. I'm not certain that we would be all that comfortable with a thrombolytic data that was confined only to -- well, I guess we have lots of trials at 28 and 35 days, but it's always nice to see the effect persist, it generally does.

Do you think that somehow this is different? I just want to clarify this, because it's

not so pertinent to this particular application, as much as what guidance, if any, should be provided to future research in this particular therapeutic area?

DOCTOR DiMARCO: Well, I think that in that setting of thrombolytic therapy, no one is looking at MI as an endpoint, or at least I don't think anyone is looking at MI as an endpoint, and so what you are looking at is the effects or modification of the myocardial infarction, and that, I think, is an appropriate long-term goal. Here, we are actually talking about preventing damage, and there are all sorts of grades of damage.

So, I think it becomes a different situation, you can't use the same long-term endpoint.

CHAIRPERSON PARKER: Marv?

DOCTOR KONSTAM: I guess I disagree a little bit, you know, and I guess I divide the question into issues of clinical relevance and issues of practicality.

I think if you wanted to seek an ideally clinically relevant endpoint nobody would pick 30 days, because a patient just doesn't care that much whether or not he or she has death or MI prevented over 30 days if that doesn't hold up over a year.

And so, I say I think to focus on the issue

of clinical relevance, ideally you'd like a longer-term endpoint, regardless of what you are looking at. And so, I don't think that this would be any different in this trial from any other.

I think the points that John and others have made speak very well to the issues of practicality of being able to document the effect and hope to see something that's relevant.

So, I think in that spirit, I think it's an appropriately chosen time endpoint. What I would like to see, and I think we do see in these data, is at least no evidence that that endpoint is being minimized over six-month follow up. We don't have the statistics that hold up well to prove efficacy at that point, as much as not having any evidence that it's going away at six months. So, I think that's what we have here.

CHAIRPERSON PARKER: So, Marv, you think that it's okay to, as the sponsor did, prespecify 30 days, but have the follow up to six months, the goal is not to achieve a p value of six months, but the goal is to make sure that the curves aren't coming together, or even worse, crossing between the 30 day point and six months, and that provides reassurance that, although the effect might be diluted, it

persists.

DOCTOR KONSTAM: Right.

CHAIRPERSON PARKER: And, but 30 days would be the best compromise to prespecify for a primary analysis for efficacy for the intervention being evaluated.

DOCTOR KONSTAM: Yes, and I wouldn't extend that necessarily to every future trial. I think that each trial, and each drug, and each intervention in each trial is going to have its own nuances with regard to the practicality of the duration of follow up.

So, I think in this case, I think I'm satisfied that the investigators chose an appropriate endpoint.

CHAIRPERSON PARKER: Ray?

DOCTOR LIPICKY: Well, I guess you have been discussing longer times, I was wondering about shorter times for primary endpoints in this kind of trial, and I guess it wasn't an appropriately -- you've addressed it fine, but I'd like just a word or two about what if you thought about 48 hours, or one week, or I don't know what the -- you know, I don't want to specify a time, but even shorter than 30 days with the intention to follow people, but that's not

where your endpoint is defined.

CHAIRPERSON PARKER: So, the concept is, if a sponsor came in and said not 30 days, we'll do the follow up for six months, but we want to specify 48 hours, is that good enough? I made that up.

DOCTOR LIPICKY: That's a fine number.

CHAIRPERSON PARKER: Okay.

Is 48 hours good enough?

DOCTOR DiMARCO: Not for a 72-hour infusion, but --

CHAIRPERSON PARKER: Okay. Let us say that just suppose the sponsor said we just want to measure events that occurred during the infusion, well, or doing the period of time that was approximated by the infusion. Not everyone necessarily gets the infusion for 72 hours.

DOCTOR LIPICKY: Or a day longer than the infusion.

CHAIRPERSON PARKER: Or a day longer, right.

DOCTOR DiMARCO: I think I could accept a shorter time period. I'd have to see the actual study and the actual device, but I think I could look at the primary endpoint at a shorter time period, when we are past the peak effect of the drug, the peak effect when

complications occur, as long as there were some longer-term data to follow up, but I think you could move that primary endpoint shorter.

DOCTOR KONSTAM: Can I say something?

CHAIRPERSON PARKER: Yes.

DOCTOR KONSTAM: My general answer to your question, Ray, would be no, that I wouldn't accept, you know, a 48 or 72-hour endpoint, in the sense that that's of no clinical relevance. And, there could be a significant possibility, depending on what we are talking about, that there would be a crossover and that you are doing something in the first 72 hours that, in fact, was negated later on over the next several days even.

So, generally speaking, I would not accept that. The only thing that I would say a little bit differently is to say that if you knew an awful lot about what is driving long-term outcomes in a particular clinical circumstance, and an awful lot about a particular pathophysiology and what a particular drug is doing, you might give in, you might say, you know what, the key question here is whether there's acute reclosure. I don't want to go into this in detail, but there could be a circumstance where you knew enough about it that you said that the 72-hour

time point, for example, really is -- I'm very confident is going to drive what's really important, which is the long-term outcomes.

DOCTOR LIPICKY: Fine. I'm comfortable with -- I know what people are thinking now, and it's complicated, and so that's okay.

You don't have to try to resolve it.

CHAIRPERSON PARKER: Okay.

There were more myocardial infarctions found by the blinded Clinical Events Committee that were identified by the investigators. What is the explanation for this discrepancy?

John?

DOCTOR DiMARCO: I think the sponsor gave us an explanation. I mean, that's an explanation for the discrepancy. I'm not happy about it. It's sort of -- it's a funny thing that, you know, we are triggering more things, we are looking at the data more carefully, but the investigators are actually on the site. So, I think their explanation is, you know, they looked at it again and they had triggers and they had specific things, it would have been nice if their investigators had been more careful and looked at the same things and had agreed. But, they gave an explanation.

The discrepancy -- I'll just stop there then.

CHAIRPERSON PARKER: Let me just state for the record, and I'm sure the committee is well aware of this, is that every trial that has an adjudication process, Clinical Events Committee, Endpoint Committee, whatever have you, always finds a discrepancy.

I guess if you didn't find a discrepancy there would be no reason to have the committee. The committee, in fact, I hate to say this to, in fact, create the discrepancies, because if there was no desire to create a discrepancy, a different point of view, there would be no purpose served by creating the committee, certainly no purpose served by saying that what the committee said mattered, and what the investigator said didn't.

So, let me just say that what is unusual about this discrepancy is that it is of such magnitude, usually the discrepancies are smaller in magnitude, and no matter how you play it it really doesn't make a whole lot of difference.

And, a lot of discrepancies, but the way, are in the classification of events, but when you do all cause it doesn't matter. What's different about

this discrepancy, which I think is the reason why it's being brought as a question, is that we're talking about 50 percent more events, which ironically enough hurt the analysis. If they hadn't had the adjudication process everyone would be walking away with a p value of .001.

DOCTOR DiMARCO: Well, you know, I think that part of what you say I agree with. I think that most of the time when you have classifying causes or classifying different events, you expect to get some discrepancies because that's often opinion.

In this situation, I got the opinion that they had very hard criteria for, obviously, death, they had all caused mortality, I didn't really care much about the different mechanisms of death, and then most of their criteria for myocardial infarction were based on hard numbers.

And, I just got the impression that the investigators didn't look very hard when they sent in the case report forms, and instead of as in many studies where a central monitor sends back to you, we noticed this, do you agree with this, they just said, we'll do that centrally, we're not going to -- there were too many centers, we're not going to bother to go back.

So, I think what you got is the first cut by the investigators, which picked up some things, missed some things, and they did it all centrally. So, I think that the explanation is the process, and average investigators.

CHAIRPERSON PARKER: Marv?

DOCTOR KONSTAM: You know, I mean, I think the easiest interpretation, you know, the quickest interpretation of what we see here is that the Endpoint Committee was, in fact, picking up things that did not have clinical relevance. I don't know that for sure, but I think that's one good explanation for why the results appear to become much more positive when you stick to the investigator's judgment.

And, I just want to comment that, you know, for future reference, and future design of clinical trials, to me these results challenge the conventional wisdom of use of the Endpoint Committee as was done in this case. It's not the first time that this has happened either, that the results of a therapy was more obviously apparently efficacious in the hands of the judgment of the investigator than the Endpoint Committee.

So, I don't know, I just wonder about that.

CHAIRPERSON PARKER: I'm just wondering one thing, Eric, maybe you can just answer one question, one of the biggest sources of discrepancy was isolated CKMB increase, no clinical symptoms, no pain, no EKG changes, one value that went up. How confident are you that that's a myocardial infarction?

DOCTOR TOPOL: An excellent question, Milt. I think we all would agree with Marvin's assessment, that, in fact, the large clinically detectable infarcts were the important ones, and there was more than a 20 percent treatment --

CHAIRPERSON PARKER: Try the mic -- yes, great, thanks --

DOCTOR TOPOL: -- but the issue about what these isolated, as you saw presented infarcts with one single enzyme and the scrutiny applied, the number of serial enzymes was unprecedented in any other trial. So, it's uncertain.

We know much more about periprocedural enzymes than we know about one isolated enzyme in an acute coronary syndrome, and whether that has any long-term prognostic significance.

So, it's highly questionable, if anything, the investigator/physician team diagnosed infarcts are much more relevant.

CHAIRPERSON PARKER: It sounds like liver function tests.

DOCTOR DiMARCO: Can I just ask one other question? When we talk about the discrepancy, you didn't go back to the investigators and they still disagreed. If the Events Committee had sent their data and said, we found this, do you agree this meets criteria, your investigators would have said yes, but you just didn't bother to do it, is that right?

DOCTOR TOPOL: That's right, but I think if you look at the actual, where the concordance is, of course, the mortality concordance was all there, and the large infarcts concordance was excellent, it was really, as Milt is bringing up, it's these isolated enzymes, the smaller infarcts were the grey zone, where naturally -- and, interestingly, those appear to be the platelet unresponsive events. You see, with this large treatment benefit, it appeared to be quite modulated by a platelet inhibitor, whereas, with the noise here it appears to be something that is not pharmacologically modulatable.

DOCTOR DiMARCO: Yes, I'm just talking about, it's really not a discrepancy between the investigators firmly feeling that these events did not meet criteria, they would have agreed if you had shown

them the data.

DOCTOR TOPOL: Yes.

CHAIRPERSON PARKER: Dan?

DOCTOR RODEN: I just have to say something in response to Marvin. I think the notion of disbanding Central Events Committees and allowing local investigators in megatrials like this to make their own judgments about what is or is not a myocardial infarction, or what is or is not some other event is a very, very dangerous suggestion.

DOCTOR KONSTAM: I didn't quite suggest that. I challenged --

DOCTOR RODEN: I don't think you did, Marvin, but I think the audience might have thought you did.

DOCTOR KONSTAM: Well then, let me make it clear, I just think that what we see here really challenges the conventional wisdom, and it ought to undergo a little bit more thought. And, if I were designing a trial, I think I might be tempted to go ahead and put the committee together and count events with that, but I might be tempted to choose, as the primary endpoint, the investigator-determined MI.

CHAIRPERSON PARKER: If you do that, I don't see any purpose for having gone through the

trouble of getting the committee together in the first place.

DOCTOR KONSTAM: Okay, I accept the point.

CHAIRPERSON PARKER: Okay.

DOCTOR KONSTAM: I don't know the answer, but I stick to just the way I said it, is I challenge the way we've been doing it up to now. I think we ought to think about it.

CHAIRPERSON PARKER: Lloyd, do you want to come up to the mic?

DOCTOR FISCHER: Probably nobody wants to hear this but a few statisticians, but it bothered my technical soul not to correct fact.

Initially, I had agreed with the FDA reviewer and Lem about this .05 level on alpha spending, but as I was sitting here I was talking, I got the boundaries, and in point of fact the final decision is not based upon 1.96, the way the boundaries are designed is that the next to last look, if the value is not at least 1.24, the z value, you actually conclude that it's harmful as it were, you stop the trial.

So, the final decision, it's not enough to have a 1.96, at the next to last look it has to be at least 1.24 and you have to have 1.96, so there is a

penalty paid, and that's why the alpha level is preserved, because it actually is -- you see what I'm saying?

DOCTOR MOYÉ: Yes, so the final analysis then is not -- the final conclusion is not based on one analysis that occurred at the end of the trial, it's based on the combined analyses at the penultimate?

DOCTOR FISCHER: Yes, yes. If the value had been, say, 1.1, the z value, in a favorable direction, by the rules would have been interesting to see the DSMB would have reacted, but by the rules the trial had to stop and actually we were supposed to declare it harmful in the other direction, which is a little bizarre.

But, nevertheless, the type 1 error is preserved because it depends upon the two values. If it only depended upon one value, everybody's intuition was obviously very -- and this was really bothering me today, it bothered me to have a public record where this was not understood.

DOCTOR FISCHER: So, just so I can clarify, if the final analysis really came in at a p value of 1.98, but you did not hit the correct level at the penultimate look, it would have been a negative trial?

DOCTOR MOYÉ: That's correct.

DOCTOR FISCHER: Okay.

DOCTOR MOYÉ: And, that's where the penalty is paid.

DOCTOR DiMARCO: Can you translate that for me?

DOCTOR FISCHER: The quick translation is, they did preserve the type 1 error at .025.

CHAIRPERSON PARKER: But, doing something different than usual.

DOCTOR RODEN: I can't resist to make the comment that we're obsessed by .05 because we were born with ten fingers, and, you know, I wonder what the statistical discussion would be had we been born with nine fingers, or 11 fingers, what magical number we would be using. I'm serious, semi-serious.

CHAIRPERSON PARKER: Tom, I really -- no, please, but don't address the nine fingers.

DOCTOR FLEMING: Not going to talk about that at all, going back to Marv's point, the CEC.

In my perspective, just thinking ahead, because we are now talking future, I think Marv has hit a critically important point. The CEC does, in my interpretation, is playing a role to achieve standardization and integrity, in essence, I would

say, of clinically relevant events.

We have to be sure that the way we are setting it up we are not capturing a large fraction of subclinical events. Did the hurdle get changed? That wasn't the intention of the CEC. The intention was standardization.

So, I think Marv's got it, it's not that we should do away with CEC, but we should be sure it's carrying out the goal of standardization of events that are at the clinical level that investigators are detecting them.

CHAIRPERSON PARKER: Tom, I'm glad you made that clarification. What was unusual about the way the CEC operated is that usually they review the events that the investigators report, but they don't seek other events.

Here, they went out of their way to seek other events, and I guess the concept is, if the issue is standardization, they should confine their attention to standardizing and potentially excluding events or disqualifying events investigators say are events, as long as the investigator initiated the process of identifying what had happened, as opposed to considering everything that the investigator did as irrelevant because the CEC, basically, is going to run

the whole thing. Is that correct? Fair enough.

John, does this discrepancy, which we've now actually discussed at great length, does it strengthen, undermine, or play no role, it's the same kind of question as number four?

DOCTOR DiMARCO: Again, I think there's a discrepancy, but because I think that this was really -- that in the end, presented with the same data, the investigators would have agreed, I don't think that this affects my interpretation of the trial.

CHAIRPERSON PARKER: Does anyone disagree with that? We've had a pretty extensive discussion on this.

Lem?

DOCTOR MOYÉ: I actually think it might strengthen mine, and I'll tell you why. I really have been concerned about this notion of unknown vital status, because the p value for the primary endpoint is so marginal. However, if I'm willing to admit that, perhaps, the adjudication of MIs was not as it should have been and, perhaps, more of these clinical MIs would have been admitted, and the p value becomes much stronger, the issue of vital status becomes less important.

So, from that rather tortured point of

view, I think I'm somewhat strengthened.

CHAIRPERSON PARKER: I don't know, it seemed very logical to me, Lem.

Marv?

DOCTOR KONSTAM: Yes, I actually agree. It does strengthen my conviction in the correctness of the primary finding, and I want to congratulate the investigators and the presenters, never once in the course of the presentation suggesting that we should look to the investigator's analysis as the one that might be more correct. They never suggested that. They wanted to stick all the time to what was the predefined primary endpoint.

Having done that, I am -- you know, the finding, I think, is bolstered by what the investigators found.

CHAIRPERSON PARKER: Sounds like there's an important lesson there, Marv.

Can we just -- this actually is an important point, so the issue of whether this discrepancy actually strengthens one's confidence is not irrelevant, given the borderline p value, issues related to unknown vital status, neither the sponsor or the investigator is claiming a strengthening of evidence, so this is a spontaneous effort on the part

of the committee in response to a question from the Agency.

So, we need to actually ask formally that question, because it may help to resolve discussions on future issues. So, John, I know you already voted, but there has been some more discussion, is there any other -- anything else that you want to say?

DOCTOR DiMARCO: I mean, the only thing I would say is that I would have preferred that they didn't split it like this, because, again, I don't really think there would have been a disagreement with the investigators and the Events Committee if they, you know, actually presented the data back to the investigator. I sort of -- I mean, this wasn't a -- or, at least this wasn't, you know, a real decision-making body of -- I don't want to, you know, impugn the abilities of Duke cardiac fellows, but, you know, they were two cardiac fellows, they checked the data, they saw if the data met these criteria, they found a lot of things that the investigators had missed. If it had been sent back to the investigator, I'm sure the investigator would have signed off and said, yes, I agree.

So, I don't think there's a big discrepancy, and I'm not sure what the benefit of

actually splitting the two was.

CHAIRPERSON PARKER: Well, the other alternative would have been that they would have sent it back to the investigator and the investigator would have said, well, I think that's ridiculous, that's not an MI.

DOCTOR DiMARCO: But, these are pretty objective criteria. I mean, there are enzyme levels which are related to normal, there are Q -- I mean, I guess you could have some disagreement on Q-waves, and there are deaths. I mean, there's not -- there's not a lot of judgment in those.

CHAIRPERSON PARKER: I don't think there was any discrepancy on deaths.

DOCTOR DiMARCO: Yes, I mean, there's not a lot of judgment in those three things.

DOCTOR KONSTAM: Yes, but, you know, what we know -- let me just challenge that a second -- what we know about myocardial infarctions we know from myocardial infarctions that were diagnosed in the clinical arena, in other words, in terms of the natural history, in terms of all that stuff, everything we know about it we know about it because a clinician diagnosed it, based on criteria, granted.

So, you know, I guess that I'm not so sure

about it being so clearly objectively definable by somebody after the fact, getting a chart review, and, you know, I think that's something of what's going on here.

CHAIRPERSON PARKER: Okay.

Well, we need to actually look at this formally, because the discussion has significance, so, Lem, I think you said it strengthens?

DOCTOR MOYÉ: That's right.

CHAIRPERSON PARKER: JoAnn?

DOCTOR LINDENFELD: What's the question, I think it plays no role.

CHAIRPERSON PARKER: JoAnn says no role.

DOCTOR KONSTAM: Strengthens.

CHAIRPERSON PARKER: Ileana?

DOCTOR PIÑA: Strengthens.

CHAIRPERSON PARKER: Dan?

DOCTOR RODEN: It plays no role, I think the problem is that they -- if they wanted to capture major clinical events than the criteria for myocardial infarction should have been different, and those Duke cardiology fellows would have then found a different number. They just followed the criteria that were established, and that's what we are asked to evaluate.

CHAIRPERSON PARKER: Okay, and my vote is

that it strengthens, so it's four to three for that, this is question 6.2, Joan.

John, would a time to first event method of evaluation have been more appropriate? Maybe I should ask that to Lem?

DOCTOR LIPICKY: Actually, you might even skip that for the sake of time, Milt, because that's totally theoretical and up in the air.

CHAIRPERSON PARKER: We'll skip it.

6.4, was there a statistically significant treatment effect favoring eptifibatide for the prespecified intention to treat analysis of death or myocardial infarction?

John?

DOCTOR DiMARCO: Yes.

CHAIRPERSON PARKER: Dan?

DOCTOR RODEN: Yes.

CHAIRPERSON PARKER: JoAnn?

DOCTOR LINDENFELD: Yes.

CHAIRPERSON PARKER: Marv?

DOCTOR KONSTAM: Yes.

DOCTOR PIÑA: Yes.

DOCTOR MOYÉ: Yes, but I'm going to say it's critically undermined by the viral status issue. I mean, the viral status issue doesn't come out in any

of these questions here, and I feel compelled to inject it. So, I have to say yes, but it really is undermined by the vital status issue.

CHAIRPERSON PARKER: Okay, and I say yes, so that's 7:0.

Was there statistically significant treatment effect for all caused mortality?

John?

DOCTOR DiMARCO: I don't recall the exact numbers, but I don't think they showed a difference -- a statistically difference in death, so, no.

CHAIRPERSON PARKER: Anyone disagree?

CHAIRPERSON PARKER: For myocardial infarction, John?

DOCTOR DiMARCO: Again, I'd have to look at the exact number, can anyone tell me what table that's in? I just want to make sure, it's where all the benefit was, but I'm not sure --

CHAIRPERSON PARKER: Before we do that, Ray, can I suggest we skip this? The reason is that it's hard to understand the validity of an analysis which focuses on the non-fatal event without including the analysis of something worse than that. Do you really want us to consider the -- I mean, I don't think that's the right thing to do.

DOCTOR LIPICKY: Okay.

CHAIRPERSON PARKER: Okay.

Was there a statistically significant treatment effect favoring the drug in the subpopulation that had PTCA, in the subpopulation had PTCA?

John?

DOCTOR DiMARCO: I actually agree with the sponsor in this, that I don't think these were randomized groups that it's hard to talk about statistics. They showed us some trends, but I don't think to describe these as statistically significant would be fair or appropriate.

CHAIRPERSON PARKER: Ray, how does one assign statistical significance to a subgroup analysis for an effect that occurs after randomization?

DOCTOR LIPICKY: Well, I think just the way you did, you can't.

CHAIRPERSON PARKER: Okay.

DOCTOR LIPICKY: The question was asked very specifically for you to enunciate that.

CHAIRPERSON PARKER: Does anyone think that we can actually address the statistical significance of question 6.5, in an appropriate fashion?

DOCTOR MOYÉ: Not in any interpretable way,

I don't think.

CHAIRPERSON PARKER: Not in an interpretable way.

Marv?

DOCTOR KONSTAM: Well, the reason for that is because it's essentially a cohort analysis, it's essentially not -- is that what the problem is?

CHAIRPERSON PARKER: It's based on an analysis of something that happened after randomization, it's not even a subgroup analysis based on a baseline characteristic.

DOCTOR MOYÉ: See, not only was it not assigned randomly, but the occurrence may very well be related to something that occurs after randomization, and so it becomes very difficult to interpret.

CHAIRPERSON PARKER: Dan?

DOCTOR RODEN: In order to answer the question, you would either have to conduct a trial in this population alone, or prespecify the population and then randomize the drug, is that what the contention is, because I think that --

CHAIRPERSON PARKER: It's not the -- this is not the right trial to answer that question.

DOCTOR RODEN: Okay.

Well, having sort of said that, rather than

asked as a question, it seems to me that there is some value in this sort of post hoc analysis, and, perhaps, in this particular instance a particularly large value because it does appear to explain the geography and, perhaps, explain the benefit in some populations and not in others.

So, I guess I agree with John, but sort of rejecting it out of hand, as seems to be going on, doesn't allow it to enter into the total package of decision-making that we're going to be asked to do in the next half hour, hour.

CHAIRPERSON PARKER: Yes, I think that, Dan, you are quite right. The problem is that the question asks us to define statistical significance, when, in fact, I think the intent of the question, Ray, help us, is to ask whether the occurrence of PTCA may have acted as a confounding factor in the interpretation of the results.

DOCTOR LIPICKY: No, and, you know, I think that the answer you gave is the answer that was expected, and that the answer -- the thing that Doctor Roden wants to discuss now is, indeed, pertinent, but is part of 15.1.

CHAIRPERSON PARKER: Okay, no problem.

DOCTOR LIPICKY: But, all I wanted to do

was to allow 15.1 to be discussed with it being clearly known that one doesn't know what the facts are.

CHAIRPERSON PARKER: Okay. It's always nice to know that we understand what's going on.

Seven, how important are the six-month follow-up data which have not been submitted to the division for review in interpreting the trial results?

John?

DOCTOR DiMARCO: Well, I think they provide some conformation that there isn't some latent adverse reaction. They haven't really been reviewed. As I said before, there's a lot of noise that occurs in that period. I think this is something that, you know, you look at if they've crossed over, or come together very rapidly, you'd be concerned about the value, the overall value of the trial, but they really don't affect the way you interpret the primary endpoint, I don't think.

CHAIRPERSON PARKER: Okay.

It's not so much how you interpret, how important are they? I think that if they didn't have the six-month data would you feel that there was something missing?

DOCTOR DiMARCO: Yes, I think that, you

know, you do have to have some long-term perspective, and six months is probably reasonable.

CHAIRPERSON PARKER: Okay.

Now, Marv echoed that earlier.

DOCTOR KONSTAM: Yes, I do feel that I'd at least like to know that there is not evidence that the effect seen at 30 days is reversing, that's what I'd like out of the six-month data.

CHAIRPERSON PARKER: So, it sounds, I just want to make sure that we're not, you know, over-interpreting this, but it sounds as if you feel that if there was something missing if the six month data weren't here, it provides some level of reassurance, maybe a considerable level of reassurance, given what the alternatives might be, that we actually think that the six-month follow-up data doesn't have to reach a p value, but you have to have it in order to take a look at what happens long term, that we actually think it's quite important.

Ileana?

DOCTOR PIÑA: I want to go back to a comment that you had made earlier about other myocardial infarction trials that have made an intervention and then looked at the mortality at six months and it has carried through, and it's true, this

is a different trial in that sense, that those interventions were after the diagnosis of infarction had been made, then you intervene.

But, I think it gives us the same level of comfort and it confirms that nothing bad or the curves haven't changed in the six-month period.

CHAIRPERSON PARKER: So, I think the consensus, Dan, JoAnn, Lem, is that actually it's quite important, is that right, Dan?

DOCTOR RODEN: Assuming that procedures for follow up are in place and there's not this ascertainment issue that Lem has worried about.

CHAIRPERSON PARKER: Yes, I mean, it has to be well done, and, you know, all the other caveats, and you really want to make sure that you have it in almost every one, if not every one.

Okay, Lem? So, the answer is, it's quite important.

Are the demonstrated incidents and severity of bleeding acceptable in this patient population? John?

DOCTOR DiMARCO: I actually have some concerns about this, simply because, you know, you are talking about treating a very large number of patients, and there doesn't seem to be any way to, you

know, assess the risk of bleeding. We didn't see any risk factors for bleeding, it's relatively low, and the significance of it, or the magnitude of it, is similar to the treatment benefit, or in the same range as the treatment benefit.

However, you know, again, I think it's acceptable, but I'm unhappy about it. Let's put it that way.

CHAIRPERSON PARKER: JoAnn, you had some comments about this earlier.

DOCTOR LINDENFELD: Well, it's probably acceptable, I just don't think we know what the long -- since we are not talking about mortality as the only endpoint, now we are balancing bleeding with MIs, and, you know, I'm concerned that this level of bleeding is substantially higher than in the dose in IMPACT, and the absolute difference is no different.

So, I guess in terms of the two studies, I'm not convinced that this amount of bleeding is acceptable, that this dose adds anything more that allows us to accept this rate of bleeding.

CHAIRPERSON PARKER: You are actually, I think, raising a couple issues, you are also raising the issue of, you know, of dose. Let me just try to just focusing on PURSUIT, because that's really what

the question is about, so only the dose which is used in PURSUIT, because that's really the only dose that PURSUIT used, that is, well, it used two doses, but the one that actually has the most experience is the high dose. Do you think that the incidence of severity, John says that he's concerned about it, I want to make sure that I quote you correctly, but that you guess it's acceptable.

DOCTOR DiMARCO: Yes, I think that, you know, would this influence my use of this drug in a clinical situation, I think, yes, it would have a negative impact on my decision, clinical decision of whether I was going to use it or not. Do I think that this is probably part and parcel of this therapy, it probably is.

CHAIRPERSON PARKER: Okay.

JoAnn?

DOCTOR LINDENFELD: Yes, I think I would agree with that, I'm still concerned by this increased level of bleeding, but it's probably acceptable. I just don't think any of us have enough information to know, probably an MI is a more important event than a transfusion, but many of these were small MIs and so I don't think we have the information to know that, but I'm concerned that in this study, at this dose,

they pretty much balance each other out.

And so, if we were to discover that transfusion were a significant event, then there isn't a positive outcome at this dose.

CHAIRPERSON PARKER: Eric?

DOCTOR TOPOL: If I could just make one point that I think is helpful here, because we are about four years into the IIb/IIIa era, and knowing the interaction with Heparin, and in this case in the context of a blinded trial, of course, adjusting Heparin downward was not possible, so while none of us would say that the transfusion rate is innocuous, and it's not something that should be ignored, the absolute numbers are low, but as we've learned from other trials, if we could lower Heparin we would see less bleeding complications.

DOCTOR LINDENFELD: But, wasn't the PTT 50 to 70 the target in PURSUIT, so that already is lower than it was in IMPACT, isn't it?

DOCTOR TOPOL: Well, but, you could be on the lower end, I mean, that is, the empiric dosing, the first dose that's used, this is a three-day protracted use of Heparin, and so the bolus, the infusion, the weight adjustment, could all be brought downward.

DOCTOR LINDENFELD: Well, it could be, but then that's a different study.

DOCTOR TOPOL: In the context of a large trial, you wouldn't be able to do that. In terms of the placebo group, it certainly can be brought downward, and, indeed, the shift to using lower and lower doses of Heparin in conjunction with various IIb/IIIa inhibitors is the way the field is moving.

DOCTOR LINDENFELD: Right, but this was lower than the current standard, this PURSUIT was 1-1/2 to two instead of two to 2-1/2 PTT, is that -- I guess IMPACT was ACT, but this was a substantially lower goal than IMPACT.

DOCTOR TOPOL: The desired range was 50 to 70 seconds, but the actual dosing, the weight adjusted dose could certainly be brought down if one had the knowledge of treating on an open basis with a IIb/IIIa inhibitor.

DOCTOR LINDENFELD: Well, except that we don't -- excuse me for just --

DOCTOR TOPOL: I'm sorry.

DOCTOR LINDENFELD: -- but we don't have the data that lowering the Heparin target further than this study then would have the same effect that this study had.

DOCTOR TOPOL: We've been through that with other trials and realize that bleeding complications are very much the interdependency of Heparin and anticoagulants and IIb/IIIa inhibitors, that's just a point -- I think the absolute numbers are not high, but it probably would be lower if this was done on an open basis.

CHAIRPERSON PARKER: Yes. The problem is that there's no way we can get there from here in this trial, because the drug was given the way it was given, and what was found in terms of risk is also linked to what was found in terms of efficacy. If one plays with the Heparin, one plays with the Heparin in both spheres.

Ileana?

DOCTOR PIÑA: I think if I interpreted the data correctly, the major number of bleeding events also occurred in the people who had the interventions, so these are the people who you would expect would bleed because they are being manipulated.

There are things in here that you can't take into consideration, such as the experience of the operator in doing the case and how difficult the patient is to get the case. So, even though I'm not happy with the fact that there has been bleeding

complications and transfusions, I don't see how you can tease this out of a multicenter trial like this.

DOCTOR TOPOL: That's actually a very key point you are bringing up, since so much of the bleeding was tied into interventions, and that's when the additional Heparin boluses are administered and ACTs are run much higher, and this is a key distinction because the bleeding is very much intertwined with percutaneous interventions.

CHAIRPERSON PARKER: Okay.

I think that we need a formal vote on this, so I guess we should just go down and hear what everyone has to say. Well, maybe we can do it in the following way, both John and JoAnn have said that they believe, although they are concerned about bleeding, and the risk to benefit issues that bleeding raises, that they believe that bleeding is acceptable, because that's what the question asks, in the patient population that was defined in PURSUIT, given the results of PURSUIT. That's a correct summary, JoAnn? Okay.

Does anyone on the committee disagree with that? Okay.

Next question, what was the effect of Aspirin on efficacy and safety risk of bleeding?

John?

DOCTOR DiMARCO: Well, for both of these next questions, I don't think we can really answer them. Such a large percentage of patients were on both Aspirin and Heparin, and we don't know why people weren't on Aspirin and Heparin, that I don't think these questions are answerable.

CHAIRPERSON PARKER: Okay.

Ileana?

DOCTOR PIÑA: I would encourage the sponsor to perform trials that would answer some of these questions and to look for the interactions between Aspirin and Heparin, and to do good dose ranging trials, the same as to find the proper dose, you don't know if there may be a dose slightly smaller than what you've used that doesn't cause any bleeding and that there's no interaction, and so I think that these have to be done with clean, good old-fashioned pharmacokinetics trials.

CHAIRPERSON PARKER: Okay.

Let's proceed to question 11, do the results of PURSUIT alone, alone, demonstrate a beneficial treatment effect of the drug when used as adjunctive therapy in patients with an acute coronary syndrome, and, again, the options available to us are

four options, this parallels the same way we tried to respond to IMPACT II, no effect, strength of evidence equivalent to less than the usual strength of evidence for one trial, equivalent to what one usually sees in one trial, or equivalent to what one sees in two trials, so one of four possible options.

John?

DOCTOR DiMARCO: I think I'd say if you take it for the entire universe of acute coronary syndromes, I'd have to say it's favorable but less than usual trial, so your step two, I guess.

CHAIRPERSON PARKER: Step two, right, or option two.

DOCTOR DiMARCO: Option two.

CHAIRPERSON PARKER: Okay.

Again, let me repeat the options, no effect, less than what is usually provided from one trial, equivalent to one trial, or equivalent to two trials.

Lem?

DOCTOR MOYÉ: Step two as well, less than one trial.

CHAIRPERSON PARKER: JoAnn?

DOCTOR LINDENFELD: I think it's equivalent to one trial.

CHAIRPERSON PARKER: Marv?

DOCTOR KONSTAM: I'll say equivalent to one trial.

CHAIRPERSON PARKER: Ileana?

DOCTOR PIÑA: I would say it's equivalent to one trial.

CHAIRPERSON PARKER: Dan?

DOCTOR RODEN: I'll say it's equivalent to one trial.

CHAIRPERSON PARKER: I also would agree, equivalent to one trial, so it's five versus two.

What is the effective dose?

John?

DOCTOR DiMARCO: Well, you know, I think this is a question that several of us have expressed concerns about, because we have some data about in vitro effects, and we have some data about in vitro measurements of platelet aggregation at these various doses, but we really don't see any gradation of clinical results.

So, I think, you know, if we want to look at the two studies that were submitted, the PRIDE and the PERIGEE study, we can get some in vitro data, and all you can is read those numbers off the curves. But, how that correlates to clinical benefit I don't

think we can tell from the data.

CHAIRPERSON PARKER: I think that it would be fair to say, though, that the evidence for PURSUIT really is only with one dose. I actually think that that's what the Agency is asking us to say. In other words, it wants us to be able to make a statement that only one dose was the source of the beneficial effect that was voted on in the previous question.

DOCTOR LIPICKY: Really, I guess, the statement is that threw away 1,000 patients. They randomized 1,000 patients and learned nothing, that's my interpretation.

CHAIRPERSON PARKER: No, Eric, it's only for you to contemplate.

DOCTOR KONSTAM: Can I ask a question that I'm not sure we saw. Did we see a final analysis of what the bleeding incidence was in the lower dose group? I don't remember seeing that. Can we ask the sponsor to comment on that? Was it an intermediate level between the placebo and --

DOCTOR HARRINGTON: Can I have slide 242, we'll show you the TIMI scale of bleeding for the three doses. This is the contemporaneous analysis, so just the analysis done in the three treatment groups at the time that the dose decision was made to

discontinue the lower dose. So, it's through the 3,200 patient analysis, to try to get a sense of comparable treatment arms, slide 242. The major bleeding, since it's not coming right up there, in the placebo group, major bleeding, 9.0, the lower dose, 10.5, and the higher dose 11.3.

DOCTOR KONSTAM: No, no, the 11.3 is at the time that the decision was made?

DOCTOR HARRINGTON: That's correct.

DOCTOR KONSTAM: And, what was the final incidence in the overall high dose group, at the end of the day?

DOCTOR HARRINGTON: Do you have that?

DOCTOR KONSTAM: It must have been in the same range.

DOCTOR HARRINGTON: It was very comparable, let me give you the exact data.

DOCTOR KONSTAM: That's all right.

DOCTOR HARRINGTON: It's 10.8.

DOCTOR KONSTAM: Okay.

DOCTOR HARRINGTON: And, 9.3 in placebo.

DOCTOR KONSTAM: So, there seems to be, perhaps, a dose response with regard to major bleeds.

DOCTOR HARRINGTON: With regard to bleeding.

DOCTOR KONSTAM: Yes.

DOCTOR RODEN: But, since you don't know efficacy in the lower dose, it's very difficult to interpret an isolated toxicity event.

CHAIRPERSON PARKER: That's true. But, there's also no power.

DOCTOR KONSTAM: I don't understand what you are saying, Dan. I mean, it seems that the higher dose -- the higher you go with the dose the higher the incidence of major bleeds, doesn't it?

DOCTOR RODEN: Right, right, but if the inference is that at the lower dose -- maybe they should use a lower dose, or maybe we should recommend a lower dose.

DOCTOR KONSTAM: No, I don't think you can say that, because we don't know anything about efficacy in that.

DOCTOR RODEN: Right.

DOCTOR KONSTAM: But, I think just in terms of the question of --

DOCTOR RODEN: Right, that's all I was saying.

DOCTOR KONSTAM: Yes, okay.

DOCTOR LIPICKY: We're still waiting to be illuminated, do you want to wait?

CHAIRPERSON PARKER: Oh, we already heard the data, so we don't need the slide.

DOCTOR LIPICKY: Okay.

CHAIRPERSON PARKER: Are the demonstrated incidents and severity of bleeding acceptable in this patient population, 11.2. We just got some --

DOCTOR LINDENFELD: We answered that, didn't we, in eight? We did that in eight.

CHAIRPERSON PARKER: Did we just do that?

DOCTOR LINDENFELD: I think that was number eight.

CHAIRPERSON PARKER: Oh, I'm so sorry. Okay. Yes.

DOCTOR LINDENFELD: It's the same question as eight.

CHAIRPERSON PARKER: No, no, no, we're in 12.

As outlined in the following table, there have been four dosing regimens of the drug studied in two major trials, that's a commentary. What is the estimate of the in vitro platelet aggregation that was achieved with each of these dosing regimens? Did I fall asleep?

DOCTOR LINDENFELD: We have 11.3 to do, I think 11.2 was the same as eight.

DOCTOR KONSTAM: It's just that 11.2 was the same as eight.

DOCTOR LINDENFELD: 11.2 and eight were the same.

CHAIRPERSON PARKER: We did 11.

DOCTOR KONSTAM: We did 11.

CHAIRPERSON PARKER: We finished 11.

DOCTOR LINDENFELD: No, we didn't do 11.3.

CHAIRPERSON PARKER: And, we discussed most of 12. Okay, good, thank you.

DOCTOR MOYÉ: Can we have some lights first? Can we have some lights, please?

CHAIRPERSON PARKER: We're okay.

DOCTOR MOYÉ: 11.3 we didn't do, did we?

CHAIRPERSON PARKER: 11.3 was 5:2.

DOCTOR MOYÉ: Beg your pardon? 11.3 --

DOCTOR LIPICKY: What are you doing, Milton?

CHAIRPERSON PARKER: Okay.

Are the results -- yes, 11.3, thank you -- are the results of PURSUIT alone sufficient basis for approval of the drug in this setting?

John?

DOCTOR DiMARCO: Is this a binary answer?

CHAIRPERSON PARKER: Yes.

DOCTOR LIPICKY: Yes.

DOCTOR DiMARCO: No.

CHAIRPERSON PARKER: Okay.

Lem?

DOCTOR MOYÉ: No, they are no.

DOCTOR LINDENFELD: No.

DOCTOR KONSTAM: No.

CHAIRPERSON PARKER: Ileana?

DOCTOR PIÑA: No.

DOCTOR RODEN: No.

CHAIRPERSON PARKER: No, so 7:0 for no.

Now, question 12. We've gone through much of 12.1 and 12.2, can you just briefly just state for the record what your answers are to 12.1 and 12.2?

DOCTOR DiMARCO: I think the in vitro data presented show that in order to achieve 80 percent inhibition of platelet aggregation in a normal calcemic environment that you have to go to the higher dose, and 182 seems to be the one that seems to have the maximum benefit according to the curves I looked at.

CHAIRPERSON PARKER: Any other discussion?

DOCTOR PIÑA: Yes. I don't entirely agree. I think that that's the dose that was selected and looked at as a subset of the PURSUIT trial, but they

never looked at it prospectively to see if it is the minimum efficacious dose within the calcium environment.

DOCTOR RODEN: And, I guess the other issue is that they do have, after the loading dose, this is the right trial, after the loading dose 50 percent of the patients did not achieve 80 percent platelet aggregation transiently, and then by 24 hours they were back to 80 plus percent, and by 48 hours up to 100 percent. So, there's certainly a window early on, perhaps, because of a kinetic fluke or other reasons, where it looks like there is room for improvement in this regimen, there would have been room for improvement in this regimen.

CHAIRPERSON PARKER: Okay.

I'm not certain that we can shed any more light on this. I think the issue has been discussed.

Question 13, compare the severity and incidence of bleeding events between IMPACT II and PURSUIT in the PTCA group, and are such comparisons meaningful? We saw that data earlier today, and what conclusions can we reach from looking at that data?

DOCTOR LIPICKY: And, I'll point out that you are throwing away the statistical hats here now, you are being doctors.

CHAIRPERSON PARKER: I don't think this is a statistical issue here. I think that the sponsor has clearly identified the fact that bleeding usually is associated with interventions, that the biggest difference between the drug treatment group and the placebo group was in the PTCA group, in terms of bleeding, and it is a common group, the sponsor, in fact, has specifically tried to link the two trials based on that common denominator, so what is being asked here is a clinical logical deducted inference, and not a p value, there's no statistics here.

DOCTOR LIPICKY: Right.

DOCTOR DiMARCO: Clinically and logically, I think that, you know, my opinion would be that these things are within the range of acceptability, but they come close to the magnitude of benefit that you see, or at least compromise the magnitude of benefit that you see, since I think even minor bleeding, to me as a clinical who refers patients for procedures, is fairly significant in terms of patient morbidity.

So, it may not be death, but I think it's something that will affect my use -- or might affect my potential use of the agent.

CHAIRPERSON PARKER: Okay.

DOCTOR DiMARCO: I really can't compare the

two studies. I think in both studies that statement is true.

CHAIRPERSON PARKER: Okay.

If the sponsor has shown data that in the PTCA group the higher regimen, the higher dose used in PURSUIT, was associated with more bleeding than the lower dose used in IMPACT II, and there has been some additional analyses that if one looked at even additional doses there may have been also a dose response relationship, do you agree that the incidence of bleeding appears to be dose related by looking at the totality of the data?

DOCTOR DiMARCO: I don't think you can compare the numbers at all, they are different populations. You have people coming in for elective procedures who get it just at the start of the procedure, people who are having their intervention 24 to 48 hours into it, I'm not sure how to compare those numbers at all, and I'm not sure which is the better regimen.

CHAIRPERSON PARKER: Marv?

DOCTOR KONSTAM: Yes, I'm not exactly sure either, and it wasn't, obviously, a single trial design to answer this question, but, you know, I mean I am struck by the fact that there was no increase in

the incidence of major bleeds in IMPACT II and there was an increase in the incidence of major bleeds in the other study, PURSUIT, and I think that the most likely clinical anyway, if not statistically valid, conclusion to be drawn by the totality of the data is that there is a dose response relationship with regard to major bleed. I can't prove that, but I think that's the conclusion that's most consistent with all the data put together.

CHAIRPERSON PARKER: I guess the question is, does the committee feel that there is a relationship between dose and bleeding risk, which can be inferred from the data that in front of us, even though there has been no definitive evaluation of that question.

Ileana?

DOCTOR PIÑA: I think it's dose related. If you look at some of the other studies that they did of platelet aggregation, you can see that there's an increase in platelet -- a decrease, rather, in platelet aggregation with the higher dose in the subset taken from the PURSUIT trial.

So, even though I don't have any direct evidence, I think we have enough inference to think that there is a dose relationship to bleeding.p

CHAIRPERSON PARKER: Dan?

DOCTOR RODEN: I disagree. I mean, I think that the populations are so different and the extended baseline platelet activation, for example, may be so different, that it's very difficult to make up a dose response relationship, except you can say that a dose of this drug increases bleeding complications, and whether a bigger dose increases them more is something I don't think I would be willing to say.

CHAIRPERSON PARKER: JoAnn and Lem, do you have any views on this?

DOCTOR LINDENFELD: I can't add anything. I think there's probably a dose relationship, but I don't think we have enough data to be sure.

DOCTOR KONSTAM: You know, I'd just like to add, you know, one point that wasn't made, in terms of comparing the mean effect on percent inhibition of platelet aggregation versus the population effect, I infer that there were a substantial number of patients that had essentially complete inhibition of platelet aggregation in this population at the higher doses.

And so, you know, I guess, just for what it's worth, I'm not surprised that you are going to get some increase in the incidence of major bleeds in there. So, anyway, that's at least consistent.

CHAIRPERSON PARKER: Lem?

DOCTOR MOYÉ: Nothing to add, Milt.

CHAIRPERSON PARKER: I'm sorry?

DOCTOR MOYÉ: Nothing to add.

CHAIRPERSON PARKER: Okay.

I guess my sense is that there is probably a relationship between dose and bleed, so I guess the committee is pretty split on this issue.

Number 14 is precisely the same question, but now an issue, the issue in front of the committee is efficacy and not safety, specifically, the magnitude of the treatment effect in IMPACT II and PURSUIT in the PTCA group. What is being asked here is not a statistical conclusion or statistically valid conclusion, it's a clinically-based inference from the available data.

DOCTOR DiMARCO: Yes. I think we've already talked about that we can't -- I don't think we can talk about the statistics in the PTCA group in PURSUIT, but clinically I do find the observations very supportive of the original trial, of the IMPACT II trial, so I do think that -- and, I think the magnitude of treatment benefits, as much as you can say, are probably roughly similar, so I think that I find the two groups, those two observations,

supported.

CHAIRPERSON PARKER: Do you think, in a parallel question to this, that -- all right, do you have any comment at all on whether the magnitude of treatment effect in the PTCA group differs from the non-PTCA group in PURSUIT, because it is in some respects the flip side of this question.

DOCTOR DiMARCO: Yes, again, I found it striking in a clinical sense that a very large proportion of the benefit was seen in the PTCA group and, again, and I mentioned this earlier when we talked about geography, it looked more like that a lot of the benefit was seen there and there was much lesser benefit seen in patients who did no undergo the intervention. And, I think that observation, even though it's not randomized, you can't really analyze it statistically, supports the data that I saw in IMPACT, which showed that there was a significant benefit in that group. So, I think that those two things tend to dovetail together.

CHAIRPERSON PARKER: Does anyone on the committee have any additional comments? These comparisons are very difficult to make, and one is always treading on very thin ice in trying to do this.

DOCTOR KONSTAM: Yes, and I'd just like to

just point out some of the differences here besides the difference in dose. You are not -- in addition to the points that were made about the problems with identifying the PTCA population, at best this is a special PTCA population that has had unstable angina and myocardial infarction, it's different duration of treatment, and the endpoints were different. So, all of this, I think, adds up to I think agreeing with John, that I don't see how you can begin to compare these two meaningfully with regard to what the different dose effects were.

CHAIRPERSON PARKER: Now, unfortunately, despite the fact that everyone on the committee says that one can't put all these data together, that is precisely what we are being asked to do in question 15. Question 15 requests us to put all of this together, all of the differences, not only in the patient population, in the dosing regimens, in the duration of infusion, difference in all the subgroup analyses, the interventions, the concomitant therapy, all of these differences, some small and irrelevant, some large and interesting, and putting together, based on a binary recommendation concerning approval and more specifically identification of patient population, treatment effect, dosing schedule and

labeling.

So, although we have all said we can't do this, that is exactly what we must do. So, the first question is a binary answer, should the drug be approved. Now, let me emphasize, all that is being requested here is yes or no. If you think it is approvable for anything, in anybody, at any dose, the answer should be yes, and you can then make all of your qualifications, and recommendations and concerns known in the sub-questions. But, if you think that you would support the approval in any patient population, and you can make that clear in questions .1 and .2, for any indication, at any dose, or a dose, then you should say yes, because what we don't want to do now is spend time saying, yes, but only in so and so. We'll get to that the next step. You should qualify your question here only if it deals with the overall issue of approval, but not the details of the approval. Is that fair?

John, would you recommend that the drug be approved?

DOCTOR DiMARCO: Yes, I can consider a scenario in which I would be led to a vote for approval.

CHAIRPERSON PARKER: That is precisely the

answer to the question which is being proposed.

DOCTOR RODEN: I agree with John, that there are scenarios under which I could be induced to vote for approval.

CHAIRPERSON PARKER: Ileana?

DOCTOR PIÑA: I agree.

CHAIRPERSON PARKER: Marv?

DOCTOR KONSTAM: I'll just say yes.

DOCTOR LINDENFELD: Yes.

DOCTOR MOYÉ: Yes.

CHAIRPERSON PARKER: Yes, so it's 7:0, and now the details.

DOCTOR LIPICKY: May I ask for a little clarification, I mean, not much, but in the preceding answers everybody -- well, I guess it wasn't everybody, but it wasn't very uniform that there were two trials that were very convincing, but yet, there's very uniform agreement that this is approvable. Does anyone find that funny?

DOCTOR MOYÉ: Ray, let me address that, because I think that each trial is weak, so why I don't address that specifically. I think that there are critical weaknesses in IMPACT, regarding the intention to treat analogy, I think there are critical weaknesses in PURSUIT regarding the vital status

issue. Both of these have marginal p values and best, and any one of the reasonable assumptions, one of many reasonable assumptions will push you over the line.

However, when I look at the data, and I ask myself for the totality of evidence, from both IMPACT and from PURSUIT, is there something here, then my honest answer is yes there is.

Now, I don't have two trials, you know, maybe I have one and a fraction, I don't know.

DOCTOR LIPICKY: Okay. I understand that, that's fine.

CHAIRPERSON PARKER: Does anyone want to add to that?

DOCTOR KONSTAM: Yes, I'd like to add to it. I mean, I think that the easiest construct that's going to wind up leading me to answer yes is to say, I see a very strong signal from one of the trials in one of the populations, and I see enough in the other trial to confirm that I really believe that signal. And, I'm sure we'll get into that in detail, but I think that's, I think, the logic that leads me to say yes.

CHAIRPERSON PARKER: Okay.

John, for what patient population would you propose that the drug be approved?

DOCTOR DiMARCO: With some reservations that we may talk about later, I would say that I find the linkage in the PTCA population fairly convincing, much as Lem says, you know, sort of like strength of evidence from the two trials.

I really don't find a lot of support from the PURSUIT data in people who did not undergo an intervention, and so I would favor, if we were going to approve it, that it would be restricted to people undergoing intervention right now.

CHAIRPERSON PARKER: Okay.

Can we have some general discussion? John is proposing approval for patients undergoing PTCA. I assume that the wording would be, PTCA in general, I guess, with or without unstable angina wouldn't be important, just PTCA.

DOCTOR RODEN: So, it's my understanding that we could use the sort of totality of data to make inferences. I support what John says.

The PURSUIT support, the conclusion of IMPACT for me, the IMPACT data provide very little support for the broad conclusion of PURSUIT for me, and, therefore, I would confine the approval to the population studied in IMPACT II or some variant thereof.

CHAIRPERSON PARKER: Ileana?

DOCTOR PIÑA: Yes. I feel the same way. After looking at the PURSUIT data, I feel much more comfortable about the IMPACT II data, because I think that confirms the use in the PTCA.

Which of the patients that undergo PTCA should be included, I'm not really certain, so I would probably stick to the population that was described in IMPACT II.

CHAIRPERSON PARKER: Marv?

DOCTOR KONSTAM: I guess I agree with what's been said. I think that the strongest argument to be made is that, as other people have said, that the PURSUIT data, that there's enough in the PURSUIT data to make me accept the IMPACT II data, that this is approvable in the setting of coronary intervention.

I'm on the fence about the other way, but I think that we have a single, what I consider a single positive trial in a broad population with probably -- and I think for a lot of reasons we are not quite clear exactly what's the population that's really driving this, and I'd like to accept the sponsor's contention that we're dealing with a single pathophysiologic entity, but I'm just not quite there.

And so, I'm not quite at the point where

I'd approve it broadly for non Q-wave MI unstable angina.

CHAIRPERSON PARKER: JoAnn?

DOCTOR LINDENFELD: I feel the same way. I just -- although I think it's logically a bit inconsistent, because PURSUIT was designed to study a strategy, still, I'm not at all convinced that patients, in the absence of their -- that you can't get the same benefit by going ahead and treating patients who have an intervention, and I'm concerned because it's inconsistent with the design of the study, but that's what the totality of data says to me.

CHAIRPERSON PARKER: Lem?

DOCTOR MOYÉ: I have nothing to add.

CHAIRPERSON PARKER: Before I go -- I just want to clarify one thing, because I guess I'm personally confused. The sponsor has presented to this committee two trials. One of them is a trial in PTCA which, despite any actions of the committee in the past, the committee has some reservations about today, and had a split vote on whether it actually liked the trial or not, and I'll use that term because it's the most non-binary term I can think of. And, it said, this committee said, it really wasn't very

comfortable with IMPACT II, and that's a trial that examined the treatment effect in a PTCA population.

The sponsor then went ahead and did a much larger trial of 11,000 patients in unstable angina and non Q-wave infarct, a trial which the committee sort of liked in a non-binary way, and which had, I guess, none of the issues of randomization, and had some issues related to investigator-determined events which gave some of us some comfort, but the patient population studied in that trial was not PTCA, the patient population studied in that trial was unstable angina and non Q-wave infarct. And, whether they got a PTCA or not was up to the clinical judgment of the investigator.

So that, the strength of the evidence is in the -- we have said earlier -- in the unstable angina and non Q-wave trial, I think we said that, that's a trial we liked better, that was the bigger trial, it was the better trial, it was the less confounded trial, it was the trial that actually is the only trial that used the dose which is being recommended. And, we're saying that that's not the basis for approval?

DOCTOR DiMARCO: Well, I'll say something here. If you recall, my votes were actually

consistent with the opinion, but I think that the fact is that if you take the whole committee's view, with IMPACT II we said that we needed some confirmation, and we got some confirmation.

If there had been a population of unstable angina in IMPACT II that was analyzed separately and had sort of the same results to support PURSUIT, we might have the same conclusion.

I think what we are saying is that, we now have something that we weren't terribly comfortable with that has not been confirmed, not perfectly, but confirmed, and so we have a weight of evidence going in that way, and we still are waiting for more evidence to show that this larger universe of people with unstable angina, non Q-wave MI, we need some more supporting data.

CHAIRPERSON PARKER: But, wait a minute, the fact that you got IMPACT II first is purely historical. They could have presented PURSUIT first. I guess I don't understand.

DOCTOR KONSTAM: Well, you know, let me comment. First of all, I would say I'm on the fence, and so I think this is a very tough decision about the approvability in non Q-wave MI, unstable angina. I guess, you know, the issue of the chronology is of no

consequence to me.

I think I have a couple of problems with approving it for the broad application of non Q-wave infarct, unstable angina on the basis of PURSUIT. The first is that we are dealing with a very broad population and a substantial amount of the endpoint, if not all of it, but a significant amount of the endpoint is being driven by the sub-population that also had a coronary intervention. So, that's one problem that I have with the broad approvability.

The second problem is in the confirmation question, and I guess we could -- nobody has commented on this, and maybe Ray wants to comment, but we could argue that because we are dealing with an irreversible endpoint of death or myocardial infarction, we might not need the same standard of confirmation. Ray is shaking his head.

DOCTOR RODEN: No.

DOCTOR KONSTAM: It's irrelevant.

CHAIRPERSON PARKER: No, I actually don't think that that's the issue.

DOCTOR KONSTAM: Okay, let me just finish then. I think that the issue is, and we haven't gotten into this in detail, in terms of rationalizing this, but I do find substantial confirmation -- some

significant amount of confirmation to the IMPACT II trial in the PURSUIT trial. Nobody has ever said that we see that the other way around. Okay. So, that's the other problem.

So, that's what's keeping me from being clear that we should approve it in the PURSUIT population.

DOCTOR LIPICKY: Right, if I can rephrase what I heard being said, sort of in my own language, what was being said was that in these two patient populations, a treatment effect was seen in each, maybe not neither of the trials being sufficient to carry the weight of the day, but that both trials sort of had a treatment effect, and that the one patient population that was in both trials, where people can walk away saying there was a treatment effect in this population and I saw it twice, was in the PTCA group, and that, therefore, one feels comfortable with the statement, well, it ought to be approved because, geez, there is a level of evidence here that says it has an effect in this disease state, but I need to name a disease state, and the only disease state I can name is to be used concomitantly with PTCA because I can't see this trial, on its own, saying for unstable angina.

That's the reasoning process that I heard, and, I mean, I must admit, maybe there's something wrong with my thinking process, but that sounds reasonable.

CHAIRPERSON PARKER: Well, I think -- let me try to -- I agree with that is what the committee is saying. The committee is saying that they have a mental concept of strength of evidence of two trials, and that that standard is considered by the committee to be persuasive, and that the data that would support an effect in two trials comes from the two trials before us, but only in the population with PTCA, and not in the broadbased population of unstable angina and non Q-wave MI. I understand that.

And, that would be the logical basis for a regulatory decision, that would be why you could say that you thought that PURSUIT was positive, but it wasn't good enough for approval.

I just think it is ironic that the larger trial, the less controversial trial, and more specifically the trial that used the dose which is being recommended, is the trial which wasn't specifically designed to study the indication which the committee says the drug should be recommended for approval.

DOCTOR LIPICKY: Correct, but that's okay.

CHAIRPERSON PARKER: I understand.

DOCTOR LIPICKY: And, I must admit this is a little bit on the strange side, and certainly is not the way in which one usually goes about this kind of decision-making, but I think the decision-making, as it has gone, is totally understandable.

CHAIRPERSON PARKER: Eric?

DOCTOR TOPOL: Yes. I'm a bit troubled by some of the discussion, because we've been reviewing a trial which is the largest ever in acute coronary syndrome, 11,000 patients, and we saw the benefit of patients before they ever got to the cath lab that was reviewed. We also saw the benefit of patients who had no intervention, that it was consistent of 1.5 percent absolute benefit, and the dose that was optimized from the first trial that was changed to this acute coronary syndrome trial.

So, to conclude that the treatment -- the therapeutic effect is only in the patients who undergo angioplasty is negated by the data. It seems that if anything it would be the other conclusion, that, in fact, this large trial, which was much more conclusive, with a treatment effect certainly emphasized by the investigator reading of the large

infarcts in patients coming in de novo, acute coronary syndrome without any intervention, whether marked benefit was shown.

DOCTOR LIPICKY: What was clearly said was if you had to conclude everything about PURSUIT from PURSUIT, then you ought to go home right now. It just ain't going to make it.

So, PURSUIT alone can't carry the day. It doesn't have enough strength to draw conclusions from it. Now, it needs something else. Okay? That's all there is.

So, what else is there? The other thing there is is PTCA, and the other thing there is, is this broad concept that everything deals with platelets, okay, and that there is some kind of thing that is a platelet thing, and it doesn't matter what you call it.

I think the committee says, go home with that notion. I can identify patient population operantly that I feel comfortable there's a treatment effect with, and the other stuff is just dreaming.

DOCTOR FLEMING: Ray, could you clarify in your second paragraph here, provided to the committed, what the intention is, it says, "The Agency specifically suggested the regulatory requirement for

independent substantiation that could be met by two studies, one in post-angioplasty, one in acute coronary syndrome, because they share the same pathophysiological basis. The draft proposal says that two such studies would support use in both clinical settings." Now, does that mean that the FDA actually meant that the acute coronary syndrome could support the post-angioplasty setting but not vice versa, or did you mean what you said?

DOCTOR LIPICKY: I didn't write that, Doctor Temple wrote that, in a draft guidance, and he implied that, in that draft guidance, that the commonality of a platelet syndrome, the commonality of platelets being important in those two patient populations, would allow one to study one patient population, the other patient population, and get approved for both.

Now, that depends on the results of the trials, and what was said here today was maybe that would have been all right if the results of both trials were really very conclusive. But, what was said here today was that neither trial was really all that convincing, so they needed -- the committee needed to attempt to make something convincing in some patient population to reach the binary approvable

level. Otherwise, it would have not been approvable at all.

CHAIRPERSON PARKER: The situation may or may not become more clear when we go through the other questions, but for the question 15.1 the vote was five for PTCA, Doctor Moyé abstained, and I voted for a more general approval.

15.2, how should the treatment effect be described?

John?

DOCTOR DiMARCO: Well, I think, you know, you describe it as the numbers that they showed.

CHAIRPERSON PARKER: I'm sorry, the intent is, what is the benefit that was derived, i.e., death, MI or intervention, or death or MI.

DOCTOR LIPICKY: Well, the results of one study were evaluated as death, MI and urgent intervention. The results of the other study were death and MI.

Now, when you describe the studies, you can describe the studies, but how will the indication read?

CHAIRPERSON PARKER: Is it for the reduction of, for example, death, myocardial infarction, or death, myocardial infarction and urgent

intervention?

DOCTOR DiMARCO: I'd leave it as death, myocardial infarction and urgent intervention. In IMPACT II, they showed that a very high proportion of the people who had urgent interventions had myocardial -- had abrupt closure, had myocardial infarctions, and I think that that was the major reason for their urgent intervention, that was a small component. So, I'd leave those three parts in there.

CHAIRPERSON PARKER: Dan?

DOCTOR FENICHEL: Milton, excuse me, there is an option here which you probably should consider as part of this question. It's something which is perennial and keeps getting shot down, but I think it's, perhaps, appropriate to bring it up again, and that is the possibility that the nature of the treatment effect might not be described. One of the things that keeps coming up is, so and so is indicated for hypertension, or so and so is indicated for congestive heart failure, we don't really say what it does in congestive failure, it's just if that you have congestive heart failure it's a good thing to take this stuff.

Now, that keeps getting rejected, and we keep going back to the trials and saying, no, it ought

to say indicated for congestive heart failure in order to reduce the frequency of hospitalization, or in order to do this or that, or whatever the other thing is that was shown in the trials.

But, we certainly have had other situations where it's been quite difficult to identify something where the committee has had this gestalt, well, it's good for you but we don't really know exactly why it's good for you, and we've been winging it in various situations, never with the solution, this is indicated for name of condition period, but, once again, that's always an option.

DOCTOR KONSTAM: Bob, you know, I think the reason that might be less of an option here, in particular, if we are looking at the angioplasty situation, angioplasty is not a condition, it's an intervention.

So, we would say it's indicated for angioplasty.

DOCTOR FENICHEL: Well, I'm not advocating that, Marvin, first of all, I'm just pointing out that it is an option, but also, you know, one could certainly write language that says it's indicated as concurrent treatment in patients who are receiving PTCA, and, you know, why should they get it? Well --

DOCTOR LIPICKY: For ischemic complications or whatever.

DOCTOR FENICHEL: Yes, something like that, and then --

DOCTOR LIPICKY: But, it wouldn't have to say --

DOCTOR FENICHEL: -- you want to find out what was found --

DOCTOR LIPICKY: -- to preserve life --

DOCTOR FENICHEL: -- read the descriptions.

DOCTOR LIPICKY: -- and decrease myocardial infarctions and keep you from cathing the patient again.

CHAIRPERSON PARKER: I think John has voted for the precise endpoint in IMPACT II, is that right? Okay.

Let's see, Marv, why don't we start on your end, what is your view?

DOCTOR KONSTAM: Yes. I guess I'd agree with that, with the alternative being some kind of wording saying, you know, clinically significant or clinically major ischemic event, as indicated by a trial that showed the effect on this combined endpoint, something of that nature might be acceptable to me.

CHAIRPERSON PARKER: Ileana?

DOCTOR PIÑA: I will vote more for the general discussion which was just presented for PTCA, and I would leave the specific endpoints out.

CHAIRPERSON PARKER: And, Dan?

DOCTOR RODEN: I'd use the IMPACT II endpoints.

CHAIRPERSON PARKER: It was fascinating, I was actually looking forward to the committee's response here, because what I was, I guess, half expecting was that the committee was going to say death and MI, and then I was going to really get upset about the inconsistency, but I guess I can't get upset about the inconsistency now because what the committee is essentially saying is that PURSUIT confirms IMPACT II, and that what drives the language here, and the whole tenor of the discussion, is that IMPACT II is really the central trial with PURSUIT confirming it, both with respect to the indication which is being recommended, that is, the patient population, as well as the treatment effect.

Having said that then, it is really interesting what you are going to say about dosing, because if the pattern has been that IMPACT -- that PURSUIT confirms IMPACT II, and you have followed this

pattern now consistently times two, then on 15.3 you've got to choose a dose.

So, John, what's the dose?

DOCTOR DiMARCO: I think this is the weakest part of the indication, because we are talking about not really knowing, or at least I can't tell what the dose response is, and we're basing -- or the sponsor is basing their request based on in vitro data.

So, I would say that, perhaps, the initial proposal would be to approve one or the IMPACT II doses and then hope that the sponsor could rapidly do some study, which didn't actually, perhaps, have to demonstrate efficacy, but at least show that there's no increased complications.

But, I would approve -- I would propose it at the start at the IMPACT II dose.

CHAIRPERSON PARKER: Dan?

DOCTOR RODEN: Without sort of crawling into other committee members -- I think it's fair to say that I'm as big a believer in in vitro data as anyone sitting up here now, but I agree with John, I think that there's very little evidence of a dose response here in clinical outcomes. I agree with all the in vitro and the in vivo, the clinical platelet

aggregation data, and so I would not sort of fall back on the 135.05 or 0.5 dose, but I would say that that's the dose that is the lowest and provides efficacy.

CHAIRPERSON PARKER: Ileana?

DOCTOR PIÑA: Yes, I concur with what Dan is saying, I would recommend the dose used in IMPACT because there was some efficacy and the risk of bleeding was quite a bit less, if I remember the percentages.

CHAIRPERSON PARKER: Marv?

DOCTOR KONSTAM: Well, I guess I'm on shaky grounds, but I guess that I'm receptive to considering the higher dose, and I understand the problem that that poses in terms of a clear rationale, given that IMPACT II is the principal trial driving it, but, you know, I do think that there -- I'm convinced by the pharmacodynamics data, and I guess that I'm not sure exactly how to word it, or how to deal with it, but I believe based on the data set that you are going to get better therapeutic effect with a higher dose.

DOCTOR DiMARCO: But, there's no --

DOCTOR KONSTAM: I know, I know.

DOCTOR DiMARCO: -- can I just interrupt for a second, there's no way that a PTCA population is going to get three days of infusion, so that, I think

we have to go with something that's within the range.

DOCTOR KONSTAM: Right.

CHAIRPERSON PARKER: John, that's a good point. If the indication is PTCA, the dosing regimen that was evaluated in PURSUIT was a specific bolus followed by specific infusion for 72 hours, but sometimes 36 because that's what was sometimes done in the U.S., but I understand --

DOCTOR KONSTAM: And, sometimes 96.

CHAIRPERSON PARKER: -- and sometimes 96, so it would be hard to stick to -- well, first of all, it would be inconsistent to pursue the dose in PURSUIT if you don't think that PURSUIT is the way you are thinking about this.

DOCTOR KONSTAM: Of course, with regard -- I mean, we understand the angioplasties were not done at the beginning of the PURSUIT infusion, so I think the data set is consistent with the belief that you could get away with a shorter infusion around the time of angioplasty, and the critical factor is likely to be the steady state that you've got around that time.

So, you know, I don't know what to do with it, because I understand that I'm on very shaky ground with regard to being able to write that down as a dosing regimen.

CHAIRPERSON PARKER: I just want to just be clear, I understand that the majority of the committee is being entirely internally consistent here, that IMPACT II is driving this, that the power is in IMPACT II, that the patient population is defined by IMPACT II, the treatment effect is defined by IMPACT II, therefore, the dosing schedule is defined by IMPACT II, and I think, by the way, particularly in terms of duration of infusion it's entirely appropriate, but this is a dose the sponsor doesn't believe in anymore.

DOCTOR LIPICKY: Yes, but that's their problem, Milton.

CHAIRPERSON PARKER: Do you think that we learned anything from PURSUIT?

DOCTOR LIPICKY: Yes, works in PTCA.

DOCTOR RODEN: Not about dose.

MS. WITHES: I have to say something, I'm Janet Withes, and what is really disturbing me about this last part of the conversation --

CHAIRPERSON PARKER: Can you identify your affiliation, sorry.

MS. WITHES: Yes, I'm a consultant for COR. What's disturbing me about this last part of the discussion is that the inference is coming out of a post-randomization subgroup, the PTCA group, which is,

in part, determined by what group the people were randomized to.

So, it feels totally -- I feel as if the logic -- I don't understand your logic.

CHAIRPERSON PARKER: I don't think that the committee is attempting to defend in precise terms the logic of this.

MS. WITHES: But, I just had to point out that the way you are taking this big study --

CHAIRPERSON PARKER: No, no, let me try, I think, Ray pursued, I think, described this accurately, the committee did not feel that PURSUIT, taken alone, was enough to get a very broadbased population indication. Part of that, by the way, is strength of evidence, part of that is concerns that many members of the committee have outlined in terms of bleeding, and the risk to benefit relationship that is defined by that.

So that, for many members of the committee, the majority of the committee, the vast majority of the committee, said I'm sorry, it just doesn't make it for us for acute coronary syndrome, and, therefore, they had two alternatives. They could either say no, please go home, you have nothing to be approved for, or, two, well, PTCA is something that the two trials

had in common, the sponsor actually made that point, and it's a more defined patient population, and it's a patient population which had at least the strength of experiences in two trials, albeit one entirely post hoc.

John, did I describe that correctly?

DOCTOR DiMARCO: Yes, I think that's exactly what we are trying to do.

CHAIRPERSON PARKER: Yes, please, you know, there's no doubt that this is an issue worth talking about for a few more minutes.

DOCTOR FLEMING: Just to briefly start off, as Janet had pointed out, looking at this from a statistician's perspective, one of the issues that concerns us greatly is that there's a fundamental difference in timing in the IMPACT trial and in the PURSUIT trial. Times zero relates to the acute coronary syndrome, and that's really the strength of the evidence from PURSUIT. It first and foremost addresses that setting with strengths, that it is a supportive, as you say, non-statistical inference.

What I'm hearing is, we have a weakly positive study in setting A, and a stronger positive study in setting B, and the inference is going to be for the indication in A, which is where you have the

weaker study, which leads me to conclude that the indication that two such studies would support use in both, italicized by you in clinical settings, was not really intended, because you are not willing to go the broader setting without really two studies in that broader setting?

DOCTOR LIPICKY: That's correct, that the literal interpretation of that statement is not appropriate. I could conceive of results, say if IMPACT I or II was really a pretty striking finding, not quite enough to win approval, but, you know, somewhere in the .01 range or something, okay, and there was no issue with respect to whether or not there was another dose that didn't look as good in the same randomized trial, and, yet, it was the same dose in terms of platelet inhibition, and then there was another trial in unstable angina that really, you know, kind of knocks your eyes out also. Then, I think that one may have been in a slightly different kind of, how am I going to put this together problem.

The problem here is that neither study is really so terrific. They both have suggestions of something going on that's relevant, and appropriate, and has benefit, but not so terrifically convincing at all, so the committee is sort of faced with having to

put it together somehow.

Ordinarily, we would not have had the questions in this order, the statement would have been, if you can't figure out who to give it to, and the committee said well we can't tell whether it works in PTCA or not in PURSUIT, okay, statistically, we don't know who to give it to, we don't know what dose to administer, my usual position would have been, how can you say approve it?

DOCTOR FLEMING: Well, just one quick comment. Listening, and it's the committee's judgment, of course, here that counts, it's the committee's view of the strengths of the studies that counts, listening, though, it seemed to me that there was masterful logic all the way up to question 15.1, and my interpretation of hearing you was that both studies were on the edge, but they were both positive and the PURSUIT trial was more positive, and where I'm struggling is the logic of not including in the indication the setting where the study was more positive.

Now, if I'm misinterpreting you, then I'm not so confused.

CHAIRPERSON PARKER: No, Tom, I think you described it accurately, but I --

DOCTOR RODEN: But, it comes down to an issue of sort of comfort levels, I think, at this point, and looking at the PURSUIT data for me, the group that I'm uncomfortable with are all those patients in other parts or the world in which the benefit was much harder to show, and who don't have the benefits, so to speak, of an intervention.

So, what I said before applies for me, and I don't want to speak for other members of the committee, the PURSUIT data set supports what I think about IMPACT, but not vice versa.

CHAIRPERSON PARKER: I think the operative word, which summarizes the committee's view here, by the way, a view I disagree with, but a view I feel that I need to summarize accurately --

DOCTOR RODEN: But, if we stay long enough you'll be a majority, Milton.

CHAIRPERSON PARKER: -- is that the operative word here is persuasiveness, and not statistical significance, and that is the two trials together create a persuasive case for a more confined indication, more restricted indication, and not for a broadbased indication. For a broadbased indication, given the large population that would therefore be eligible for treatment, they would like to see either

a much more persuasive PURSUIT II in that indication, or two trials in that indication with the same kind of borderline result.

Would that be an accurate summary?

DOCTOR HARRINGTON: I guess that I'm troubled at two levels. I'm troubled at the clinical trialist level, and I'm trialed as a practicing clinical level. As a clinical trialist level, it seems to me that the discussion is punishing the investigators, punishing the sponsor, for doing a large clinically applicable trial, as opposed to picking two small sort of pathophysiologic-based trials and coming with 2.05 answers that would meet approval, but not necessarily be applicable to clinical practice.

CHAIRPERSON PARKER: No, no, I'm sorry, that would really not be accurate. All the committee is saying is the broadbased trial, as it is constructed now, is something that the sponsor deserves a tremendous amount of credit for, what the committee is saying is that based on its own view its the first of two steps.

DOCTOR LIPICKY: Well, can I add to what you just said?

I don't think there's punishment associated

with anything. To me, at least, from my perspective, the problem is that the effect, maybe the dose is still wrong, the effect is small, so that you needed to have a very large patient population to be able to come up with the statement that, in fact, you were better than placebo, and that although one is willing to grant that PURSUIT found that, that it was not a trial that would stand alone and get a binary regulatory judgment on that basis.

Now, that's either because the patient population is wrong, that is, that isn't what you ought to try to do to people with unstable angina, that could be, or that there's something wrong with that treatment, its effect is too small. Okay?

Now, from that single trial, you can't unravel that complexity. It's not a punishment to anything, it's nice he took it on, but the question is, does it really -- maybe you shouldn't do this to people with that state. Okay?

Now, so to not be punishing, in particular, since you were following the bosses' guidelines, but the committee doesn't care about that, okay, that wasn't -- their judgment -- they don't even know that -- okay, they were saying, I can't detect the treatment effect here, but I want to be sure that the

patient population that will receive this treatment is a patient population that I feel comfortable that will really be better than placebo.

And, granted that you can pick some holes in their being able to say that in PURSUIT II, okay, they couldn't say that in PURSUIT II, they'd send you home again. So, don't take that away from them.

But, the broader indication of unstable angina just can't be supported by that one trial, it just won't work.

DOCTOR HARRINGTON: I've agreed with much of what you've said, but I just want to take issue with two things, and I know that the time is late here, the first of which is the comment, Doctor Lipicky, that it's a small effect, and I would propose that to expect anything other than modest incremental benefits in a disease where people are treated with beta blockers, Heparin, Aspirin, ACE inhibitors, lipid lowering therapy, et cetera, would be unrealistic.

So, I think that these are real effects that are being measured.

DOCTOR LIPICKY: No, no, no, that wasn't a disparaging comment, if it was a big effect you wouldn't need 11,000 patients.

DOCTOR HARRINGTON: That's right.

DOCTOR LIPICKY: Okay.

So, it's just the fact that you need to do large trials means that it's not a very big treatment effect.

DOCTOR HARRINGTON: But, my second point --

CHAIRPERSON PARKER: The operative word is not small, because your points are well taken, the operative word is persuasive, that deals with the strength of evidence, not the magnitude of evidence, which largely deals with whether the p value is at the level of .05 or more persuasive than that.

DOCTOR HARRINGTON: And, along those lines, to look at the persuasiveness, since we seem to be honing in on the subgroups, I'd say let's hone in on the subgroup that we all -- in the context of which we all practice, and that's the North American data.

The North American data is over 4,000 patients, it's larger by several fold than most angioplasty trials that we all see and that we base our practices upon. In the North American data, there is a treatment effect of a fairly sizeable magnitude, bigger than the 1.5 percent in the group of patients undergoing intervention, in the group of patients without intervention.

And so, in that 4,000 patient subset that

we all practice in, there's treatment benefit in both groups, and I think Mike nicely showed when you only look at the events after angioplasty, in fact, looking at the odds ratio, the point estimates are almost parallel. And, to say that the treatment benefit is mostly in angioplasty, particularly, in the context of that we are all practicing, where 80 percent of the patients are going to heart catheterization, where 40 percent of them are undergoing angioplasty, is just wrong.

DOCTOR LIPICKY: You have a single demonstration of that, and that single demonstration was something like 43 events.

DOCTOR HARRINGTON: A small number of events.

DOCTOR LIPICKY: Yes.

Now, you don't expect anyone to believe that that establishes a fact, do you?

DOCTOR HARRINGTON: If we look at the overall 4,000, the event rate is about 12-13 percent.

DOCTOR LIPICKY: No, no, just --

DOCTOR HARRINGTON: The difference of events.

DOCTOR LIPICKY: -- just the population you talked -- the event you are talking about, that's just

not very persuasive, it won't fly on its own.

DOCTOR HARRINGTON: But, I would argue then that you step back, you look at the IMPACT II data, to confirm that common pathophysiology of a platelet-dependent disease state that benefits from the treatment.

If anything, I would submit that what clinicians need is a drug that people come into the emergency room, you don't know the treatment strategy, you treat them empirically --

DOCTOR LIPICKY: Could be.

DOCTOR HARRINGTON: -- up front.

DOCTOR LIPICKY: Could be, but your trial doesn't establish that.

CHAIRPERSON PARKER: Bob?

DOCTOR FENICHEL: Yes. I just wanted to see if this helps in thinking about this, in making an analogy to a situation which is a plausible one, and, perhaps, members of the committee will say, yes, this is what they are doing.

Let us suppose that a sponsor came forward with a drug for severe hypertension, and showed in a relatively small population that they seemed to reduce the incidence of strokes and other ill effects of severe hypertension, but it was just one study, it was

sort of borderline significance and so on.

Now, the same sponsor proposes that this is a drug which is useful for reducing events, an outcome reducing measure in patients with all degrees of hypertension, down, indeed, to normal tension, and so, a large trial is done because the effect there will be small, and what's shown is that, yes, it does seem to be better, but, once again, not that damn much better, despite the fact it's a very big trial, it's a more difficult population in whom to show any benefit.

So, what one has is a weak result in the very large population, a weak result from the earlier trial in the small and easier to study population, and now one might say, look, it does seem to be true, this is a good drug for severe hypertension, but the more radical claim of being a drug of benefit to us all, even normotensive people, in reducing the incidence of blood pressure related events, that would be a difficult claim to make, and would certainly not be given on the basis of the data I've just hypothesized.

Is that a fair analogy to the position that the committee has taken?

CHAIRPERSON PARKER: Gee, I don't know.

DOCTOR LIPICKY: I think it's more -- I think maybe, I mean, but that's very complicated, what

is the severe hypertension analogy, is that unstable angina or angioplasty?

DOCTOR FENICHEL: It's angioplasty.

DOCTOR LIPICKY: Okay, so the implied clinical meaning is not the same, because angioplasty doesn't have the acute coronary syndrome, potential heart attack, morbidity and all that stuff associated with it, but it might be worth discussing further, but I don't know that we have to now.

CHAIRPERSON PARKER: All right.

Let me say that 15.4, which is what should the labeling say about concomitant use of Aspirin, Heparin, my assumption is that since they were used this was on top of that, that the labeling would reflect it was on top of that, I'm not certain there's anything in particular one needs to say.

DOCTOR LIPICKY: No, there's nothing particular. You could recommend this is what was used, but nobody knows whether you should.

CHAIRPERSON PARKER: All right.

I think we've covered all of the questions, and we are adjourned.

(Whereupon, the meeting was concluded at 4:02 p.m.)